Peptic Ulcer Disease in Older Adults

Introduction

Current epidemiological data suggest that individuals over 65 comprise the fastest-growing segment of the North American population. Currently around 12% of the population is in this category, but this is expected to grow to 20% by 2030. Declining birth rates, premature mortality, and worldwide socioeconomic advances are allowing humans to achieve unprecedented longevity. The aging process confers certain unique traits to the pathophysiology, clinical manifestations, and treatment of most diseases, and peptic ulcer disease (PUD) is no different. In North America, the annual incidence of new gastrointestinal bleeds is roughly 500,000, with over two million recurrent events. Age-related changes in the physiology of the gastrointestinal tract, multiple comorbidities, atypical responses to pain and symptoms, and polypharmacy impart tremendous variability and complexity to PUD in this cohort, making this entity particularly difficult to diagnose and treat (Table 1). Additionally, the outcomes for PUD among older adults are worse than for younger individuals, often due to diagnostic uncertainty, delayed therapy, and decreased physiologic reserve.

This review will examine the specific issues relevant to the older adult population that predispose them to peptic ulcer disease. The often atypical presentations of PUD in older adults will be discussed, as well as an approach to diagnosis. Finally, appropriate management strategies will be reviewed.

Issues Specific to Older Adults

Age-Related Physiological Changes

An age-related decline in physiologic reserve across nearly all organ systems is a well-established concept in gerontology. The gastrointestinal tract also undergoes functional decline in both motility and secretory capacity, predisposing older individuals to a variety of pathologies. Although these factors may not affect the pathogenesis of PUD directly, they can result in symptoms that confound the presentation of PUD. Within the esophagus, the upper esophageal sphincter opening may be impaired, and both primary and secondary peristalsis is often nonpropulsive and of diminished amplitude when compared with younger cohorts. Other changes include increased xerostomia, decreased salivary clearance, and increased consumption of medications causing esophageal erosions or reduced lower esophageal sphincter (LES) tone (such as bisphosphonates and calcium channel blockers), all of which significantly increase the risks of gastroesophageal reflux and esophagitis.

It has also been shown that advancing age is independently associated with delayed gastric emptying, although the clinical relevance of this finding has been questioned. It is generally believed, however, that the rising prevalence of comorbid diseases impairing the autonomic nervous system and, ultimately, gastric motility (such as diabetes mellitus, Parkinson’s disease, and chronic renal failure) may be the
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Table 1: Issues Specific to Older Adults in Peptic Ulcer Disease

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The incidence of NSAID-induced infection is a common entity worldwide, averaging 30% prevalence rates in industrialized regions and 90% in developing nations. Its role in gastric ulcer disease and duodenal ulcer disease is firmly established, and it has been widely accepted as a carcinogen in gastric adenocarcinoma and mucosa-associated lymphoid tissue (MALT) lymphoma.11

In North America, the prevalence of H. pylori infection increases with age, from 10% at age 20 up to 50% by age 60.12 The infection is acquired in childhood and the increased prevalence seen with age is due to a higher acquisition of infection in those whose childhood occurred in the early 1900s because of poorer sanitation at the time. In addition, immigrants from developing countries will have higher prevalence rates. Given the increased prevalence of the infection with age, the older the individual, the higher the likelihood of an H. pylori-related etiology to his or her dyspepsia (e.g., PUD). Indeed, when encountering dyspepsia in the older cohorts, the clinician must not underestimate the synergy between Helicobacter infection and nonsteroidal anti-inflammatory drugs (NSAIDs), commonly used agents among older adults, in the development of gastropathy, peptic ulcer disease, and its complications (Figure 1).

Comorbidity

Life expectancy in the Western world has been extended largely through advances in ongoing therapies for chronic incurable conditions. The byproduct of this progress is an aging population in which any single patient may harbour multiple comorbidities. These conditions affect the etiology, diagnosis, and therapy of PUD. For example, neurologic conditions that are seen with increasing frequency in advanced age, such as cerebral infarction, dementia, and Parkinson’s disease, interfere with individuals’ ability to seek treatment and communicate with physicians, which delays diagnosis and treatment. As patients may be consuming an array of pharmacotherapies, clinicians should be aware that certain agents may exacerbate PUD. For example, PUD is often potentiated by acetylsalicylic acid (ASA) or NSAIDs that are indicated for cardiovascular or rheumatologic purposes. Many older adults also take anticoagulants for thromboembolic arrhythmias or metallic cardiac valves, further increasing complexity and risk of mortality in bleeding ulcers. Finally, outcomes in complicated peptic ulcer disease are adversely affected by poor physiologic reserve in multiple organ systems.

Polypharmacy

Although older adults comprise close to 20% of the North American population, they are responsible for the consumption of nearly half of all medication sales.13 The increased burden of disease among older people is typically accompanied by polypharmacy and drug-drug interactions. It has been well documented that anticholinergics (such as tricyclic antidepressants) and opioids, two commonly prescribed classes of drugs among older adults, cause delayed gastric emptying and decreased peristaltic amplitudes throughout the remaining gut.14

One of the largest risk factors for peptic ulcer disease in North America, across all ages, is the use of NSAIDs, and older adults are major users of these medications in both prescription and over-the-counter (OTC) forms. Coronary artery disease and osteoarthritic conditions form the basis for significant ASA or NSAID consumption in this age group. Approximately 40% of older adults take at least one prescription NSAID per day and some literature reports nearly seven times the frequency of OTC NSAID use when compared with younger cohorts.3,15

Besides being recognized as a cause of peptic ulcer disease, NSAIDs also increase the risk of peptic ulcer complications by three- to fivefold.15 The incidence of NSAID-induced peptic ulcers requiring hospitalization or resulting in fatality increases linearly with advancing age, independent of comorbid conditions.16 One potential explanation for the increased frequency and severity of NSAID gastropathy in the older population is that prostaglandin production in the gastric mucosa is significantly lower than in younger controls.17 The gastric epithelium produces mucus and bicarbonate-rich

Most relevant causes of delayed gastric emptying among older adults. Collectively, these diseases disrupt the normal motility patterns by altering the intragastric distribution of chyme, slowing the frequency of the antral migrating motor complex, and interfering with normal propulsive contractions of the proximal small bowel.5

Acid secretion among older adults has been a controversial topic in the literature. Although one would expect reduced gastric acid secretion given the higher rate of chronic gastritis and gastric atrophy found in older adults, multiple studies have been conducted comparing basal acid outputs between different age groups, with contradictory results.10 At the present time, it is generally accepted that gastric acid levels in older adults are not significantly different from younger cohorts.
Figure 1: Gastric Ulcer Due to *Helicobacter Pylori*

Simple columnar epithelium
Simple columnar cells line the inner surface of the stomach wall and secrete mucous that will protect the epithelium from acids and enzymes along the lumen’s wall.

Chief cell and pepsinogen
The largest number of chief cells are located at the bottom of the gastric gland. They secrete pepsinogen, which will be converted by the gastric acids in the lumen to activate proteolytic enzyme, pepsin. Pepsin aids in the cleaving of amino acids.

Parietal cell and intrinsic factor/HCL
Parietal cells are mostly located along the proximal end of the gastric gland. They secrete intrinsic factor, which is responsible for vitamin B$_{12}$ absorption. Parietal cells also secrete hydrochloric acid (HCL), which helps break down cell walls and connective tissue of microorganisms, and promotes chief cell secretion.

G cell (enteroendocrine cell) and gastrin
These cells are most abundant in the gastric pits located in the antrum region of the stomach. G cells are dispersed among chief cells and parietal cells. Activated by the intake of food, G cells will stimulate the secretion of the chief cells and parietal cells. G cells also encourage smooth muscle activity in the stomach wall.

1. *Helicobacter pylori* not only increase the acidity level of the stomach but also invade the mucosal layer of the epithelium. With their spiral-shaped bodies, they force their way under the mucous layer of the epithelium where they are protected from the harmful effects of the gastric acid and enzymes.

2. *Helicobacter pylori* will attach to the epithelium and release phospholipase and proteases, which further damage the epithelial lining. The invasion of *Helicobacter pylori* will spread deeper into the wall of the stomach.

3. The most damaging effects of *Helicobacter pylori* are the exposure of the lamina propria to gastric acids and enzymes, causing the wall to erode and potentially rupture, forming an ulcer, and the invasion of the bacteria into surrounding blood vessels. The cytotoxin-associated gene (cag A) found within *Helicobacter pylori* has been associated with severe gastritis, gastric ulcers, gastric cancer, and lymphoma.
Much of this excess mortality is attributed to two separate phenomena. The first is the relative lack of typical symptoms in the patient; among demented individuals, a perforated peptic ulcer may present as a further depression in mental status or entirely asymptomatic. It is also not uncommon for older adults to present with unexplained anemia or hypotension, entirely unrelated complaints (such as a fall), or none at all. The second phenomenon is the diagnostic delay on the part of the physician, often as a result of older patients’ lack of classical symptoms (such as a fall), or none at all. Clinical responses such as fever, leukocytosis, and peritoneal signs, often as a result of cerebral infarcts and dementia may interfere with the appropriate acquisition of a relevant history and physical examination suggestive of an ulcer. Third, the higher likelihood of NSAID use and *H. pylori* infection in advanced age groups increases the pretest probability of peptic ulcer disease in suspected patients. Fourth, comorbidities that limit physiologic reserve and complicate peptic ulcer disease leave little room for diagnostic and therapeutic delay.

Endoscopy is the preferred diagnostic tool for peptic ulcers; it allows the physician to anatomically locate the lesion, stage the bleeding risk, and rule out concurrent active *H. pylori* through mucosal biopsies. Additionally, endoscopic biopsies must be obtained in cases of gastric ulcer to rule out gastric adenocarcinoma, which is of particular concern for older adults given the higher prevalence of this condition with advanced age. Finally, endoscopy is the only modality that allows therapeutic intervention in bleeding peptic ulcers. The sensitivity and specificity for the diagnosis of a peptic ulcer using endoscopy approaches 100%, which is superior to double-contrast barium study. However, in cases where cardiorespiratory reserve is poor and safe endoscopy is not assured, double-contrast barium studies can be performed instead. If a peptic ulcer is suspected on this imaging modality, the diagnosis of *H. pylori* can be made on the basis of a urea breath test.

### Treatment of Peptic Ulcer Disease in Older Adults

As in all populations with active peptic ulcer disease, therapy is anchored by three strategic cornerstones: maximize acid suppression, eliminate NSAIDs or mitigate their effect, and eradicate *H. pylori* if present (Table 2).

#### Acid Suppression

Raising intragastric pH is most effectively achieved with proton pump inhibitors (PPIs). The existing oral formulations achieve essentially equivalent acid suppression with relatively

### Symptoms of Peptic Ulcer Disease in Older Adults

Typically, the symptom complex attributed to peptic ulcer disease is characterized by localized burning epigastric pain, often awakening the individual from sleep. Other commonly reported symptoms include nausea, vomiting, anorexia, heartburn, and relief or aggravation of symptoms with food. Epigastric pain is consistently reported by more than half of patients under the age of 80; conversely, a complete lack of epigastric pain in almost two-thirds of individuals over 80 with peptic ulcers has been demonstrated. When peptic ulcers perforate, the outcomes for older adults can be disastrous, with mortality rates more than triple that of younger cohorts. Much of this excess mortality is attributable to two separate phenomena. The first is the relative lack of typical symptoms in the patient; among demented individuals, a perforated peptic ulcer may present as a further depression in mental status or entirely asymptomatic. It is also not uncommon for older adults to present with unexplained anemia or hypotension, entirely unrelated complaints (such as a fall), or none at all. The second phenomenon is the diagnostic delay on the part of the physician, often as a result of older patients’ lack of classical clinical responses such as fever, leukocytosis, and peritoneal signs.

The reasons for these discrepancies in symptomatology in older adults are not entirely clear, but it is reasonable to theorize that contributing factors include altered neurological processing of visceral stimuli, cognitive impairment and the subsequent inability to communicate with health care professionals, decreased immune reactions to infection, and concomitant immune-suppressing medications (such as steroids).
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Key Points

Age-related changes in the physiology of the gastrointestinal tract, multiple comorbidities, atypical responses to pain and symptoms, susceptibility toiatrogenic factors, and polypharmacy impart complexity to peptic ulcer disease (PUD), complicating diagnosis and treatment.

The gastrointestinal tract also undergoes functional decline in both motility and secretory capacity, predisposing older individuals to a variety of pathologies.

The clinical relevance of delayed gastric emptying is still under question.

*Helicobacter pylori’s* role in gastric ulcer disease and duodenal ulcer disease is firmly established; the older the individual, the higher the likelihood of an *H. pylori*-related etiology to his or her dyspepsia (e.g., PUD).

Comorbid conditions affect the etiology, diagnosis, and therapy of peptic ulcer disease.

Peptic ulcer disease is often potentiated by NSAIDs that are indicated for cardiovascular or rheumatologic purposes, and anticoagulants increase the complexity and risk of mortality in bleeding ulcers.

Symptoms attributed to PUD include localized burning epigastric pain, often awakening from sleep, as well as nausea, vomiting, anorexia, heartburn, and relief or aggravation of symptoms with food.

The sensitivity and specificity for the diagnosis of a peptic ulcer using endoscopy approaches 100%.

The aims of PUD therapy are threefold: maximize acid suppression, eliminate NSAIDs or mitigate their effect, and eradicate *H. pylori* if present.

safe side effect profiles, making them desirable for use in older populations. Drug absorption and metabolism may be of theoretical concern with PPIs. The resulting alterations in intragastric pH caused by PPIs have been implicated in both increased and decreased absorption of several medications such as digoxin, ASA, and certain antifungals. Inhibition of cytochromes, such as CYP2C19, may interfere with the metabolism of several medications, such as warfarin, diazepam, and phenytoin, although clinically significant effects are extremely rare with these agents.

A recent case-control study compared more than 13,500 hip fracture patients to more than 135,000 controls, all over the age of 50. The odds ratio (OR) for hip fracture in PPI users of more than one year duration was 1.44, and for patients on high-dose regimens (i.e., twice-daily), the OR was calculated to be 2.65. This risk appeared to increase with prolonged exposure to PPIs. The effect was hypothesized to be due to the inadequate solubilization (and therefore absorption) of calcium in the acid-suppressed state, resulting in osteopenia. Use of PPIs should therefore be in appropriate doses and duration.

In addition, there are some data suggesting that the hypochlorhydric state induced by long-term PPI use (more than four years) may result in statistically significant decreased serum cobalamin levels, although still remaining within the normal range. However, there is no evidence to suggest that long-term PPI use leads to the clinical sequelae of B12 deficiency, and it is generally felt that routine monitoring or B12 serum is not required.

Regarding the proposed increased risk of community-acquired pneumonia and colitis due to *Clostridium difficile*, current data remain controversial and relegated to the domain of significantly ill patients with multiple comorbid conditions. The benefits of these agents in PUD, however, clearly are superior to any potential adverse effects.

**NSAIDs**

NSAID or ASA-induced or potentiated peptic ulcer disease poses a particularly challenging therapeutic dilemma to the physician due to the high prevalence of coronary artery disease and arthritic conditions among older adults. In general, NSAIDs or ASA should be discontinued if possible in patients with active ulcers. If this is not possible, coadministration of a PPI should be initiated when the NSAID or ASA is reintroduced at a later date. Studies on this strategy indicate that ulcer healing rates approach 80% at four weeks and nearly 90% at eight weeks.

Concerning NSAID use for rheumatic conditions, COX-2 inhibitors may be substituted for traditional COX-1 inhibitors, although the increased risk of adverse cardiac outcomes must be considered.

In older adults with multiple risk factors for peptic ulcer (e.g., assigned to both ASA and an NSAID), it would be reasonable to add a PPI or misoprostol for primary prevention of peptic ulcer. Alternatively a COX-2 inhibitor can substitute for a nonselective NSAID, if there are no cardiovascular contraindications, but for patients at most risk of peptic ulcer (e.g., an older adult with previous peptic ulcer bleed requiring an NSAID), it would be prudent not only to switch to a COX-2 inhibitor but also to add a PPI.

*Helicobacter Pylori*

Current recommendations are to test for and treat *H. pylori* in adults with peptic ulcer disease, and this includes the older adult population. The recommended regimen for older adults is identical to other adults, namely a 7–14 day course of two antibiotics (such as clarithromycin and amoxicillin) and a PPI. This treatment offers an excellent
eradication rate (>80%). Confirmation of eradication is as per any age group best with urea breath test unless an endoscopy is warranted for another reason, such as confirmation of gastric ulcer healing. Among older adults, issues to consider include compliance due to the number of pills involved, drug-drug interactions for the components of the therapy, and the risks of increased clostridium difficile infection, particularly if the therapy is initiated in hospital.

The testing and treatment of H. pylori infection for prevention of peptic ulcer in patients initiating long-term ASA or NSAID treatment has been suggested by the Canadian Helicobacter Study Group, but this recommendation remains slightly controversial because it is based on less than optimal evidence.

Conclusion

Older adults are predisposed to higher risks of peptic ulcer disease, largely on the basis of increased NSAID use, a higher prevalence of H. pylori infection, and decreased gastric prostaglandin production. When this phenomenon is combined with the lack of the typical presenting symptoms, peptic ulcer disease becomes particularly difficult to diagnose and treat. Multiple comorbidities and coexisting polypharmacy further complicate this entity, hence the high rate of morbidity and mortality of PUD in this population. Currently, there is no easy, rapid, and noninvasive test to determine the presence of an ulcer. The physician must always harbour a high index of suspicion and actively pursue this potential diagnosis in order to treat in a timely fashion and avoid unnecessary adverse outcomes.

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References