

# Gastroesophageal Reflux Disease and Barrett Esophagus in the Elderly



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## KEYWORDS

- Gastroesophageal reflux disease • GERD • Barrett esophagus
- Esophageal adenocarcinoma • Elderly

## KEY POINTS

- The early diagnosis and optimal management of elderly patients is vital to the delivery of high quality care in an aging patient population.
- Maintaining a low threshold is essential given atypical presentations and increased repercussions of a delayed or missed diagnosis.
- Contextualizing a discussion regarding management of complications and treatments in the elderly should be personalized and account for patient comorbidities.
- Novel minimally invasive screening, surveillance and treatments of GERD and Barrett's esophagus have allowed us to manage a larger at-risk elderly patient population.

## INTRODUCTION

An aging population is a global phenomenon, with minor regional variations in the demographic transition. Average life expectancy continues to increase and many countries are experiencing population contraction and decreasing fertility. Nine percent of the world's population was older than 65 years in 2015, and that proportion is projected to increase to 17% by 2050.<sup>1</sup> This pattern is evident in North America, which is second only to Europe as the oldest region, with 21.4% of population being 65 years or older. In fact, 20 million individuals will be older than 85 years in 2050.<sup>2</sup>

This demographic change is also affecting the way we diagnose and manage the most common upper gastrointestinal indication for primary care physician clinic visits, gastroesophageal reflux disease (GERD). GERD is defined as reflux of gastric contents

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into the esophagus, oropharynx, nasopharynx, larynx, or lungs with resultant symptoms and complications.<sup>3</sup> Heartburn, manifest as epigastric burning with radiation to the chest or neck, is a common typical symptom.<sup>3</sup> It is estimated that one-fifth of the adult Americans population experiences heartburn at least once a week, with 15 million suffering from symptoms on a daily basis.<sup>4</sup> Original studies indicated increasing incidence of GERD with age, with 6% to 17% of the elderly US population reporting these symptoms.<sup>5</sup> GERD also accounts for nearly a quarter of primary care physician visits for patients 65 years or older,<sup>6</sup> and it is the sixth most common disorder in nursing home residents.<sup>7</sup>

Various studies have attempted to identify the frequency of esophageal mucosal injury in GERD, and overall incidence for esophagitis varied from 6.4% to 15.5% in population studies.<sup>8</sup> Severe reflux esophagitis was more prevalent (37%) in patients 70 years or older in a population study of 12,000 patients compared with 12% in patients 21 year old or younger.<sup>9</sup> This likely underrepresents the at-risk cohort, given impaired sensory function with age. Patients 65 years or older have shown to have decreased and delayed reporting of balloon esophageal distention<sup>10</sup> and sensitivity to esophageal acid perfusion.<sup>11</sup>

Not only is GERD more common, but the presentation is often atypical and more severe in the elderly. Atypical symptoms include dyspepsia, epigastric pain, anorexia, dysphagia, odynophagia, weight loss, anemia, and belching.<sup>3</sup> In fact, only 40% of patient 65 years or older reported typical symptoms in an evaluation of 600 patients with erosive esophagitis.<sup>12</sup> In another study, older patients with Barrett esophagus had symptom scores that were comparable with that of control patients without reflux.<sup>12</sup> Hence there are significant clinical implications to a delay in diagnosis. A systemic review and meta-analysis identified more severe patterns of reflux and esophagitis in the elderly despite no change in GERD symptoms.<sup>13</sup>

Beyond esophageal injury, elderly patients are also prone to GERD-associated aspiration, which carries a significant risk of morbidity and mortality.<sup>14</sup> Manometric changes in the upper esophageal sphincter (UES) have included lower baseline pressure, decreased relaxation, and increased pharyngeal contractility.<sup>15</sup> Moreover, the UES response to reflux is reduced.<sup>16</sup> Laryngopharyngeal reflux (LPR), with or without classic GERD, is associated with a significantly higher economic burden, with 5438\$ per person compared with 971\$ for GERD.<sup>17</sup> Although it is likely that LPR is more common in the elderly, the absence of classical symptoms and limited objective testing in the population makes it difficult to ascertain true incidence. Associated symptoms include reactive airway disease, chronic cough, laryngitis, hoarseness, and voice change.<sup>18</sup>

## **PATHOPHYSIOLOGY**

The pathophysiology of GERD in the elderly is multifaceted. Changes include structural and dynamic changes at the level of the lower esophageal sphincter (LES), increased incidence of hiatal hernias that are often larger than younger cohorts, increased gastric refluxate, ineffective esophageal clearance, and luminal stasis in the setting of esophageal dysmotility.<sup>4</sup> Other factors include limitation in activities of daily living and musculoskeletal postural changes.<sup>6</sup>

Larger hiatal hernias and lower LES pressures have also been reported more frequently in an elderly population.<sup>19</sup> Frequent transient lower esophageal sphincter relaxation (TLESRs) are part of pathophysiological underpinnings for the increased frequency of GERD. There is no clear association between age and TLESRs,<sup>20</sup> but the polypharmacy commonly seen in the elderly includes many medications that have

been associated with more frequent TLESRs. These include nitrates, calcium channel blockers, benzodiazepines, anticholinergics, antidepressants, and lidocaine.<sup>21</sup> Broadly combined into presbyesophagus, the subtle changes in the esophageal body are less clear. Retrospective reviews of various institutional experiences associate aging with major motility disorders.<sup>22–25</sup> Elderly patients with endoscopic or impedance evidence of GERD are more likely to have an esophageal motility disorder on manometry (44% 70 years or older vs 13% 17–39 years old)<sup>26</sup> and lower rates of swallow-induced peristalsis on impedance study. Increasing age was also associated with more frequent reflux but less severe reflux episodes.<sup>20,27</sup> The clinical implications of cellular changes in autopsy studies indicating decrease in ganglionic cells and increased lymphocytic infiltration in esophageal biopsies when compared with young individuals are uncertain.<sup>28</sup> Yet similar changes have been noted in major esophageal motility disorders.<sup>29</sup>

In addition to mechanical stasis the reflexive ability to increase salivary bicarbonate is diminished in the elderly despite the absence of change in volume and baseline bicarbonate levels.<sup>25</sup> This weakened neutralizing salivary secretion is paired with increased gastric refluxate in the setting of a growing epidemic of obesity, which has not spared the elderly and makes reflux worse via multifactorial pathways.<sup>30</sup>

## TESTING

The low risk of complications from esophagogastroduodenoscopy (EGD) are often pitted against the odds of an endoscopic finding that would validate the diagnosis or ideally change medical management. Many would favor of an empirical proton pump inhibitor (PPI) trial instead of an EGD in many scenarios. This is most applicable to a primary care setting and young otherwise healthy patient population. PPI trial is an acceptable option, as it is available, noninvasive, and inexpensive, with sensitivity ranging from 68% to 83%.<sup>4,11,31</sup> Typically, EGDs are recommended to assess refractory symptoms or to patients who are unable to wean off medical therapy or patients who are unable to wean off medical therapy or to assess complications.

Given atypical symptoms or absence of symptoms in the elderly and a higher prevalence of severe disease and complications, EGD is encouraged earlier in the elderly, as it helps complete a thorough workup and avoids delay in diagnostic care. Although there is no guideline recommendation to support EGD in this group yet, visual evaluation has the added advantage of assessing the presence of and degree of esophagitis and identifying and treating GERD complications including strictures and Barrett esophagus (with or without malignancy).<sup>3</sup>

Esophageal functional testing with pH and impedance is the most informative test in GERD. Metrics of disease continue to be defined and validated, with esophageal acid exposure time being the most reliable thus far. Impedance monitors allow for a detailed functional analysis of distal and proximal esophageal reflux events.<sup>32</sup> These results should be interpreted with caution, as normative values may not apply to a geriatric population.<sup>33,34</sup>

Radiographically, a well-performed double contrast esophagram complements an endoscopy and can identify a subtle stricture that would have otherwise been missed. Esophagrams may identify changes associated with esophagitis yet they lack the necessary sensitivity for a screening test.<sup>3</sup> Although they are financially disincentivized and being performed less frequently, esophagrams

continue to play a role in tailoring antireflux surgery and improving outcomes via the careful assessment of gastroesophageal junction (GEJ) anatomy relative to the diaphragm and other anatomic details. They can also add informative data on patients with postoperative symptoms. Additional predictive metrics include barium tablets, where a delay in the 13-mm tablet may suggest a tight fundoplication.<sup>35</sup>

Evaluating LPR is challenging. Beyond the field of view of a standard EGD, structural evaluation with laryngoscopy is essential but findings typically associated with GERD are nonspecific. Functional testing such as esophageal pH/impedance has poor sensitivity. Oropharyngeal pH testing and salivary pepsin evaluation are not as widely adopted due to unclear utility. More accurate sensors and indices that are objective and validated are needed to help guide some of the more targeted chemical and pH testing of proximal pharyngeal reflux.<sup>36</sup>

## TREATMENT

### *Lifestyle Modifications*

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The efficacy of lifestyle modifications is not limited to young patients. Elderly patients can benefit a great deal from minor changes in their dietary and sleeping habits. The latter includes head of bed elevation, ideally by using wedge mattress inserts.<sup>37–39</sup> Moreover, appropriate utilization of positive ventilation in patients with obstructive sleep apnea has been shown to help reduce nocturnal reflux.<sup>40</sup> Effective dietary changes include avoiding late evening meals and meals with a high fat content.<sup>41</sup> Finally, weight gain increases frequency and severity of GERD. Hence, weight loss is a recommended and effective measure to reduce reflux.<sup>30</sup>

### *Medical Therapy*

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Antacids are very effective in the rapid treatment of pyrosis symptoms (typically 30–60 minutes) but their long-term efficacy is limited. They are readily available over the counter in various formulations that have comparable efficacy. Uniquely a few formulations have the added benefit of an antireflux barrier in the form of an alginate raft.<sup>42</sup> Although antacids are typically considered safe, there are some side effects that are more concerning in elderly patients. Antacids can interfere with absorption of other essential medications, have undesirable effects on bowel habits (aluminum and calcium containing agents worsening constipation), and may increase overall salt intake (with preparations containing sodium bicarbonate). Milk alkali syndrome can occur, albeit rarely, with increased dosing. This is often exacerbated by concomitant use of angiotensin-converting enzyme inhibitors, thiazides, and nonsteroidal anti-inflammatory medications. Finally, there are some reports associating aluminum containing antacids with Alzheimer disease.<sup>43</sup>

Antihistamines (H<sub>2</sub> receptor antagonists [H<sub>2</sub>RAs]) are a step-up therapy. They are commonly used for reflux and are effective over an extended period of time, yet they are less potent than PPI and have a shorter duration of action. In a meta-analysis of 7000 patients, erosive esophagitis was healed 84% versus 52% on PPI versus H<sub>2</sub>RAs.<sup>44</sup> Although there is some concern over tachyphylaxis, the effective use of H<sub>2</sub>RA as solo therapy or additive therapy for nocturnal symptoms is common. Beyond recent concerns for impurities in ranitidine formulations, there are some concerns of mental status changes associated with H<sub>2</sub>RAs. These are most relevant to patients with renal and hepatic impairment. Cimetidine is less commonly used than other H<sub>2</sub> receptor antagonists in part because of its effect on cytochrome enzymes, and this can have significant downstream consequences for elderly patients with

polypharmacy, particularly in combination with medication with narrow therapeutic windows.<sup>45</sup>

Potent suppression of gastric acid production with PPI is the most effective medical treatment of GERD regardless of age. Although plasma clearance decreases with age, no dose deescalation is necessary in elderly patients.<sup>46</sup> Pantoprazole and esomeprazole pharmacokinetics seem to be relatively unaffected by age.<sup>47</sup> Direct comparison between various PPI has indicated slight superiority for esomeprazole in healing of mucosal erosion,<sup>48</sup> and omeprazole-sodium bicarbonate in achieving prolonged intra-gastric suppression,<sup>49</sup> but there are no substantial clinical differences.<sup>3</sup>

Management of GERD in the elderly predicated on the principle of the least invasive intervention with the greatest potential benefit. Common side effects of PPI are mild and include headaches, nausea, abdominal pain, change bowel habits, rash, and dizziness. Typically considered a mainstay of treatment of GERD, PPIs were widely prescribed and likely overutilized. There is momentum to move away from a standardized approach, given growing literature on potential long-term side effects.<sup>50</sup> This literature includes retrospective cross-sectional studies, randomized control trials, and meta-analysis with conflicting data. Side effects can be grouped into malabsorptive, infectious, and other rare complications.

Gastric acid suppression theoretically leads to vitamin B12 deficiency through an inability to liberate intrinsic factor. This is more profound in elderly who are at a greater risk of pernicious anemia. Associations between vitamin B12 deficiency and PPI use have been limited to case series and retrospective reviews.<sup>51–53</sup> Current guidelines and expert opinion do not advocate for serum vitamin B12 measurements.<sup>4</sup> Other concerns include decreased absorption of divalent minerals such as calcium and magnesium. The concern with calcium pertains to the risk of poor bone health, which is particularly concerning in postmenopausal women who are at risk of osteoporotic fractures.<sup>54</sup> There are also some retrospective studies associating PPIs with increased cardiovascular and renal events. Beyond checking vitamin D levels, there are no data to support additional testing.

In the absence of gastric acid barrier there is a theoretic increased risk of infection. Community-acquired pneumonia and *Clostridium difficile* infections have been most widely studied. Respiratory infections are postulated to be related to increased bacterial colonization in the upper gastrointestinal tract.<sup>55</sup> Despite the publication of randomized control trials and meta-analysis the results continue to be mixed.<sup>54</sup> The risk with enteric infections, particularly *C difficile* is more pathophysiologically plausible and data supported.<sup>56</sup>

Dementia and altered mental status have been suggested in retrospective cohort studies but not validated in prospective case control studies.<sup>57–59</sup> Autoimmune interstitial nephritis is a well-categorized entity that represents a very rare complication of PPI use.<sup>60</sup>

An 8-week course of any PPI once a day achieves healing of esophagitis in 73% to 91% of patients.<sup>61</sup> Elderly patients may require greater acid suppression for esophagitis healing,<sup>62</sup> and relapse in the elderly can be as high as 90% on stopping PPI therapy.<sup>63</sup> Nonetheless, overprescribing PPIs and the failure to discontinue them affects 66% of hospital admissions. It likely represents a significant proportion of the huge health care cost associated with reflux. Early appropriate discontinuation of PPI and H2A has now become a quality metric with several societal and institutional initiatives.<sup>64</sup>

Several prokinetics have been considered and evaluated in the treatment of GERD, with the purported mechanism of increasing gastric acid secretion and improving LES tone. Until recently the only FDA-approved prokinetic agents were erythromycin and

metoclopramide. The dopamine antagonist, metoclopramide, has been shown to increase LES pressure and improve gastric emptying.<sup>65</sup> There is a black box warning for idiosyncratic reaction of irreversible tardive dyskinesia. Moreover, it has been associated with muscles tremors, spasms, agitation, anxiety, insomnia, and drowsiness in up to one-third of patients.<sup>66</sup> Domperidone is not available in the United States and shares many prokinetic properties with metoclopramide but has a higher safety profile given limited central nervous system interaction.<sup>67</sup>

### ***Surgical Therapy***

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In patients who forego medical therapy (in part due to polypharmacy) or are refractory to medical therapy, surgical repair of the hiatal defect and the creation of a more efficient antireflux barrier is possible. A laparoscopic fundoplication is the standard of care. In addition to decades in refinement of surgical technique, personalized surgical planning with a presurgical evaluation is widely adopted. Structural examination includes esophagram and endoscopy, whereas preoperative functional testing includes pH/impedance testing, manometry, and a gastric emptying study. Randomized control trials have identified comparable efficacy between PPI therapy and laparoscopic fundoplication.<sup>68</sup> Results have been durable over 5 years<sup>69</sup> with only a minority requiring reinitiation of PPI.<sup>70</sup> Durability beyond the first decade and need for redo fundoplication are less applicable in an elderly population.<sup>19,71–73</sup> Although some data suggest that elderly are more susceptible to earlier complications,<sup>74–76</sup> studies with open and laparoscopic fundoplication show no increase in mortality or morbidity in this age group,<sup>77–79</sup> which further supports the need for careful patient selection and a complete and thorough presurgical evaluation.

### ***Endoscopic Therapy***

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Endoscopic antireflux therapy provides a middle ground between surgical and medical therapies and has been a target of extensive biomedical advancement. Many devices with promising early data have gone out of stock due to a lack of durable benefit and unacceptable complications. Available options include augmentation of the GEJ through submucosal radio frequency ablation scarring (Stretta) and endoscopically placed gastroesophageal junction t-fasteners (transoral incisionless fundoplication).<sup>4</sup> These minimally invasive interventions have varying degrees of evidence and societal support. At present insurance coverage and careful selection of patients will allow us to best identify a subset of elderly patients who would benefit from such interventions and avoid some of the risks associated with surgical or medical therapy.

## **BARRETT ESOPHAGUS**

In addition to esophagitis, strictures, Barrett esophagus, and esophageal adenocarcinoma (EAC) are potential complications of long-term GERD.<sup>80</sup> Incidence of all seems to increase with age.<sup>81–85</sup>

Barrett esophagus is defined as metaplastic growth of specialized intestinal epithelium that appears as columnar mucosa in the distal esophagus on an endoscopic evaluation. The incidence of Barrett esophagus seems to increase with age,<sup>86</sup> in part due to pathophysiological barrier breakdown at the level of the esophagogastric junction and progression in size of the hiatal hernia. This validates epidemiologic data indicating peak incidence of EAC in the sixth and seventh decade of life.<sup>87</sup> The sensitivity of symptoms to suggest Barrett esophagus is low; in fact almost one-third of elderly patients are asymptomatic.<sup>88</sup>

Various societies have adopted an age threshold (commonly 50 years) as a risk factor that is incorporated into determining patients who should undergo screening. These guidelines also advocated for an age limit on screening.<sup>89–91</sup> This is partly due to increasing comorbidities and nonesophageal cancer-related mortality in the elderly. A discussion regarding likelihood of survival over the next 5 years is recommended. There is limited literature on the life expectancy of elderly men with Barrett esophagus. In a recent cross-sectional study of 4252 veterans, a quarter of patients were 80 years old or older. One-third of them had limited life expectancy at the time of their Barrett esophagus diagnosis and a quarter of them died within 4 years of diagnosis.<sup>92</sup>

Dysplasia remains the only readily available and reliable predictor of progression to adenocarcinoma.<sup>93</sup> Misattribution of inflammation to dysplasia is common<sup>94</sup> and might be more challenging in the elderly given concomitant esophagitis. In addition to less frequently causing symptoms, esophagitis is typically more severe in the elderly.<sup>9</sup> It is therefore strongly encouraged that histologic risk assessment is delayed until esophagitis is healed. On medical optimization the interval for surveillance depends on degree of dysplasia: 3 to 5 years for nondysplastic Barrett esophagus and 6 to 12 months for Barrett esophagus with low-grade dysplasia (LGD). Endoscopic ablation is an acceptable alternative in patients with LGD with reasonable life expectancy. Patients with high-grade dysplasia are uniformly recommended to undergo endoscopy therapy. The guidelines do not recommend different intervals based on age.<sup>89–91</sup>

Esophagectomy remains a treatment of high-grade dysplasia and for endoscopically untreatable adenocarcinoma. There is significant increased morbidity and mortality associated with an esophagectomy in the elderly despite advances in technique and postsurgical care.<sup>95,96</sup> Because of the advent of effective and durable endoscopic esophageal sparing procedures, there are arguments to extend the age limit of screening and testing.<sup>90</sup> In fact studies have suggested a preferentially improved 2-year survival rate for elderly patients treated endoscopically.<sup>97</sup> The outcomes of endoscopic and surgical therapies are significantly improved in high volume centers.<sup>98</sup> This is most applicable in elderly patients in whom early detection of complications and management of comorbidities play a significant part.

Identifying a potent chemoprophylactic agent that can reduce the progression to advanced dysplasia and cancer has been actively sought. Many medications with antiinflammatory or antineoplastic potential have been evaluated. Aspirin (ASA) has chemoprophylactic properties against various gastrointestinal cancers.<sup>99,100</sup> A recent prospective multicenter trial, AspECT, found the greatest benefit was for a combination of high-dose PPI and ASA. It should be noted that although ASA toxicity is low, there is a risk for bleeding, intestinal ulceration, and strictures.<sup>101</sup> Several randomized trials have recently found nearly double the risk of bleeding with no to little cardiovascular benefit in patient receiving ASA chemoprophylaxis.<sup>102</sup> USPSTF now recommends a more tailored role for ASA that accounts for the weight of various bleeding risk factors.<sup>103</sup> Although chronic PPI use for chemoprophylaxis use in Barrett esophagus has more evidence behind it, the use of ASA solely for chemoprevention in Barrett esophagus remains controversial.

## SUMMARY

As our population continues to age, the early diagnosis and optimal management of patients with GERD becomes paramount. Maintaining a low threshold for

evaluating atypical symptoms in this population is key to improving outcomes. Should patients develop complications including severe esophagitis, peptic stricture, or Barrett esophagus then a discussion of medical, endoscopic, and surgical treatments that accounts for patient's comorbidities and survival is important. Advances in screening, surveillance, and endoscopic treatment of Barrett esophagus have allowed us to dispel concerns of futility and treat a larger subset of the at-risk population. Given that GERD persistently accounts for high per patient and health care costs, it is essential we continue to improve the quality of our health care delivery.

## DISCLOSURE

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