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## GASTROESOPHAGEAL REFLUX DISEASE IN THE ELDERLY: AN UPDATE

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### ABSTRACT

Analyzing medical issues related to the elderly patients, particularly in the gastroenterological sphere, Gastro-Esophageal Reflux Disease (GERD) seems to be a disease that reaches an important role in terms of diagnosis and therapy, as well as adversely affect the quality of life of these "frail" patients. Comorbidities that affect these patients often lead to reduce the importance of this disease, which in fact, not infrequently, it is difficult to identify because of mild symptom picture compared to younger patients. It is important to remember that GERD, although in most cases provokes only vague dyspeptic symptoms, can also lead to serious complications, such as bleeding especially in patients with impaired hemostasis, aspiration pneumonia, or even to cancerization of Barrett's esophagus. In addition, there are several factors favoring GERD, for example polypharmacy carried out for other conditions, which can modify the physiology of the anti-reflux mechanisms. This review addresses the problem of GERD, analyzing it in all its aspects.

**Key words:** Gastro-esophageal reflux disease, Proton-pump inhibitors, Elderly.

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### Introduction

The aging of population is an important social, economic and political issue. It has been estimated that in 2030, approximately 21% of the population will be aged over 65 years; thus will further increase the number of geriatric patients and health demand<sup>(1)</sup>.

In particular, to date, it has been estimated that about half of outpatient visits made by general practitioners in the elderly regards gastroenterological-related problems. In elderly, Gastro-Esophageal Reflux Disease (GERD), is very common among gastrointestinal diseases, unusually more severe than young patients frameworks. In the elderly, frequently, GERD is under-diagnosed, usually because of the chronic proton-pump inhibitors (PPIs) therapy prescribed as protection for iatrogenic drug damages, such as antiplatelet and nonsteroidal anti-inflammatory drugs (NSAIDs)<sup>(2-4)</sup>.

GERD is a consequence of pathological reflux of gastric and/or duodenal contents in the esophagus, which can induce a spectrum of clinical condi-

tions ranging from simple symptomatic reflux to esophageal mucosal injury (esophagitis) and even complications such as stenosis and Barrett's esophagus<sup>(5-9)</sup>.

The study of the different GERD framework in elderly is complicated by several factors. Esophageal sensitivity seems decrease with aging and elderly patients usually underestimate and tolerate symptoms that the younger ones do not. The coexistence of other diseases, such as chronic obstructive pulmonary disease (COPD) and coronary heart disease (CHD), may be confused or exacerbated by GERD<sup>(10)</sup>.

Furthermore, a long-term therapy with drugs such as calcium-antagonists and nitrates in elderly patient with cardiac disease and/or high blood pressure, facilitates the GERD onset, as these drugs reduce lower esophageal sphincter (LES) muscle tone and consequently determining incontinence. Cholecystectomy, very frequent in elderly, especially women, is another possible risk factor for a constant duodenal-gastric reflux, which can easily spread to the esophagus. Generally, in elderly, most

common symptoms are regurgitation, dysphagia, chest pain and respiratory symptoms rather than heartburn<sup>(11)</sup>.

Using PubMed and Medline, we performed a research using as keywords “GERD”, “elderly”, “acid reflux disease”, “gastroesophageal reflux”, “hiatal hernia”, “antacids”, “PPIs” and “endoscopy”.

## Epidemiology

The considerable clinical variability of GERD, clearly evident in elderly patients, creates a lot of difficulties in collecting accurate epidemiological data. As regards prevalence data, studies about typical symptom of “heartburn” and endoscopic diagnosis of esophagitis have been performed<sup>(12,13)</sup>.

General population complains of monthly heartburn between 21% and 36%, and between 5% and 7% of daily one. In a recent study performed on 559 elderly patients, 8% of males and 15% of females had symptoms suggestive of gastroesophageal reflux at least once a week. Symptoms reported at least once a month in 54% of men and 66% of women. In addition to reflux typical symptoms chest pain, dyspepsia, and respiratory symptoms were associated too<sup>(8,14,15)</sup>.

A GERD risk factor is given by the increased frequency of overweight or obesity both in general population and in elderly one, for, at least, two reasons: increased lipids intake raises acid secretion and reduces the gastric emptying time; moreover, increasing of abdominal pressure facilitates the reflux<sup>(16-18)</sup>.

Locke et al. report that both atypical chest pain and acid regurgitation, are present in 20% of elderly patients (aged over 75 years old) at least once a week, and in 59% at least once a month. Esophagitis rate ranges between 1% and 22%, with a higher frequency of mild grades compared to severe or complicated ones<sup>(14)</sup>.

It has been observed that 32-43% of patients with GERD did not present endoscopic lesions, while 50-60% of patients with typical symptoms and 60% of patients with atypical symptoms had an endoscopic diagnosis of esophagitis. Respiratory symptoms were reported in 57% of patients with esophagitis compared with 33% of those without this last one<sup>(9,19)</sup>.

In elderly patients subjected to endoscopy for abdominal symptoms and/or anemia, esophagitis was diagnosed with stage ranging from II to IV in

18% of cases; 29% did not have typical symptoms of esophagitis and only 24% of patients with regurgitation had also esophagitis. Zhu et al. showed that reflux disease and esophagitis incidence is higher in symptomatic elderly patients compared to younger ones (66% vs. 46.9%). Furthermore, patients with reflux symptoms have worst esophageal injury (esophagitis III/IV 20.8% vs. 3.4%)<sup>(13)</sup>.

Moreover, in elderly is frequent hiatal hernia, a GERD closely related condition.

As well as the GERD prevalence increases with age, becoming particularly high after 50 years old, so the incidence increases significantly (mean age 55 years old) (Figure 1). Even esophagitis severity increases significantly with aging, as it reported in an endoscopic study in which 75% of patients with esophagitis was represented by “sixties”. In this regard, a recent U.S. study has confirmed this trend showing an increase in hospital admissions for esophagitis, esophageal ulcer and stenosis (Figure 2)<sup>(11,20)</sup>.

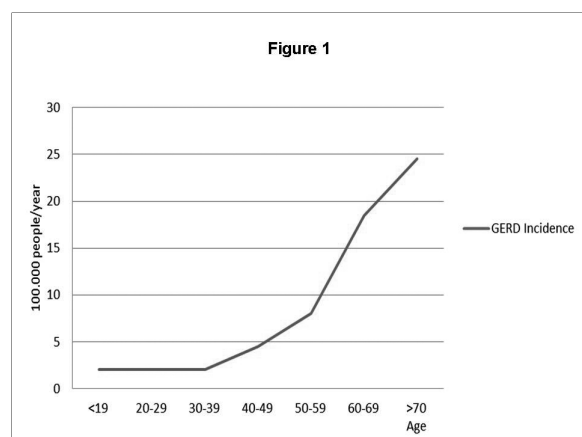


Figure 1: GERD incidence

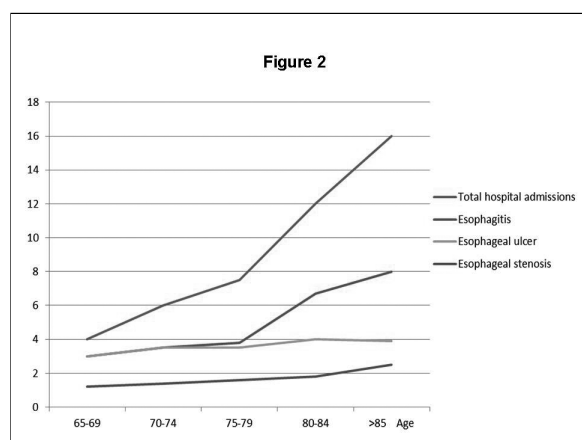


Figure 2: Hospital admissions for esophagitis, esophageal ulcer and stenosis

GERD Complications are more common among the elderly. In particular, the esophageal stenosis and

Barrett's esophagus reach their maximum frequency between 50 and 70 years old. Prevalence of esophageal stenosis in patients with esophagitis ranges between 10% and 20%, while incidence is estimated around 8%. Barrett's esophagus, characterized by the presence of columnar epithelium replacing normal squamous epithelium in the third lower esophageal, is considered a pre-neoplastic lesion, which neoplastic transformation risk is from 30 to 125 times higher than the normal epithelium; adenocarcinoma onset within a Barrett's esophagus has a prevalence ranging between 8% and 15%, with an average age around 60 years old<sup>(7,21,22)</sup>.

### Natural history

GERD natural history data were collected in the last two decades with the introduction of diagnostic techniques such as esophageal manometry and 24h pH-metry. GERD is a clinical syndrome with a chronic-relapsing course, characterized by low annual mortality (0.42/100.000); the main causes of death are esophageal bleeding (52%) and aspiration pneumonia (35%)<sup>(23,24)</sup>. Decease, due to these complications, is more frequent in patients with severe concomitant diseases (neurological or psychiatric disorders, heart disease, alcoholism, asthma, chronic bronchitis, stroke), conditions often found in elderly patients<sup>(25,26)</sup>.

Therapy discontinuation usually results in symptoms recurrence. A prospective study showed that 70% of patients exhibit GERD symptoms within three years after therapy suspension, and a prolonged remission of symptoms occurs only in a minority of patients (30%). However, reduction or disappearance of symptoms does not always coincide with reflux disease disappearance: patients tested 17-32 years after diagnosis, treated with medical therapy, have shown that though 75% had symptoms improvement, about 66% showed pathological reflux signs (pH-metry positive, esophagitis, Barrett's esophagus)<sup>(27,28)</sup>.

Most of the patients with a durable remission changed lifestyle, took antacids as needed, but most of all cycles of 4-8 weeks with anti-secretory drugs, while in others is necessary a continuous control by medication and in rare cases, non-responders to therapy with high PPIs dose, an anti-reflux surgery<sup>(29,30)</sup>.

### Physiopathology

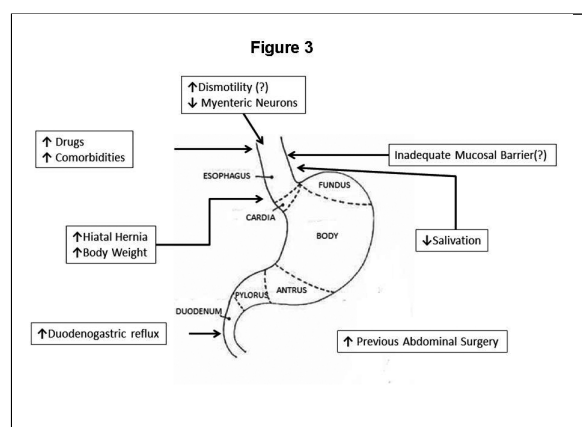
GERD study in elderly must consider the physiological changes of organs and systems due to aging.

Although the old concept of "presby-esophagus" (a condition characterized by reduced contractile capacity, LES incomplete relaxation and esophageal dilatation) can now be considered passed, is however undeniable that in elderly can be observed several changes in esophageal motility. Recent studies have demonstrated that elderly exists:

- a reduced LES pressure;
- a delay in esophageal relaxation after swallowing;
- a decrease in secondary esophageal peristalsis (propulsive waves induced by swallowing);
- an increase in tertiary peristalsis (propulsive asynchronous waves)<sup>(31-33)</sup>.

Recently, these changes have been related to the presence of typical elderly comorbidities, such as diabetes mellitus, neurological disorders and polypharmacy, while healthy elderly show only insignificant changes in esophageal motility than younger people<sup>(34-36)</sup>.

Pathogenesis of GERD is multifactorial (Figure 3) but is mainly related to motility abnormality, which results in a prolonged and repeated contact of the esophageal mucosa with the gastric contents and/or duodenal one<sup>(37,38)</sup>.



**Figure 3:** GERD physiopathology

The main pathophysiological event is represented by the insufficient functioning of the anti-reflux barrier represented by LES and muscular bundles of the diaphragm surrounding the esophagus. LES tonic contraction is the main mechanism to prevent the reflux, and manometric studies have clearly shown that reflux episodes are linked with

LES relaxations. These are mostly found in post-prandial period and are favored by gastric distension, representing about 80% of all reflux episodes<sup>(39-41)</sup>.

In elderly patients is frequent and clear the difficulty to maintain the upright position (especially in the post-prandial period) because elderly patients are often:

- bedridden for acute or sub-acute pathologies (it is known that only a few days of bed rest in elderly lead to GERD with esophagitis);
- affected by an immobilization syndrome resulting from disabling neurological or neuro-vascular disease;
- carriers of severe kyphoscoliotic deformations of spinal column<sup>(42,43)</sup>.

All these conditions increase the number and duration of episodes of nocturnal reflux, with a GERD enhancement, also due to a natural reduction of esophageal clearance and saliva (alkaline) production during sleep. In the elderly there is a hypotonia-hypotrophy of diaphragm and gastro-phrenic ligaments that, in addition with hiatal hernia, contribute to determine LES incontinence<sup>(44)</sup>.

The gastric acidity, nevertheless, plays a decisive role on the appearance of symptoms and mucosal lesions, and it is established that increasing the time during which pH remains <4, the damages caused by reflux are worse<sup>(45)</sup>.

More recently other factors have been studied such as the epithelial barrier, the mechanisms of cellular transport and local blood flow and has been emphasized their role in maintaining the esophageal epithelium integrity. Other factors contribute to promote reflux such as delayed gastric emptying, which, however, does not seem to have different patterns among the young and healthy elderly, reduced tension of esophageal wall and a decreased excitatory cholinergic innervation<sup>(6,47,49)</sup>.

Multidrug therapy (Table 1), with drugs that have as target the esophagus (Table 2), and comorbidities (Table 3) seem to play an important role in elderly GERD genesis. These drugs can trigger or enhance GERD mainly through two mechanisms:

1. direct injurious action on esophageal mucosa. In this category are included: NSAIDs, aspirin, potassium salts, iron salts, steroids, bisphosphonates. These drugs should be avoided or administered with caution in elderly patients who have: a reduced esophageal motility (leads to an increased time of contact between the ingested capsule and esophageal mucosa); a decreased resistance of esopha-

geal mucosa: several factors as salivary secretion, production of salivary and esophageal EGF (epidermal growth factor) and esophageal prostaglandins and sub-mucosal blood flow, are often deficient in elderly patient; a difficulty in maintaining an upright position.

2. reduction of LES pressure. In this category: dopaminergic drugs, benzodiazepines, tricyclic antidepressants, calcium channel blockers and nitrates<sup>(35,48-51)</sup>.

Reduced pressure of LES	Direct mucosal damage
Theophylline	Tetracycline
Progesterone	Quinidine
Anti-cholinergics	Potassium salts
$\beta$ -agonists	Iron salts
Dopamine	NSAIDs
Diazepam	Bisphosphonates
Opioids	
Calcium Channel Blockers	
Nitrates	

**Table 1:** Drugs that provoke direct or indirect alteration of the esophagus.

Diuretics	68%
Anti-hypertensive	61%
Laxatives	59%
Inotropes, anti-arrhythmics, vasoactive	56%
Bronchodilators, mucolytics, analeptics	47%
NSAIDs, salicylates	46%
Sedatives, hypnotics	36%
Antacids, anti-ulcer drugs	29%
Anti-platelet	21%
Steroids	17%
Oral hypoglycaemic agents, insulin	15%
Other	43%
None	5%

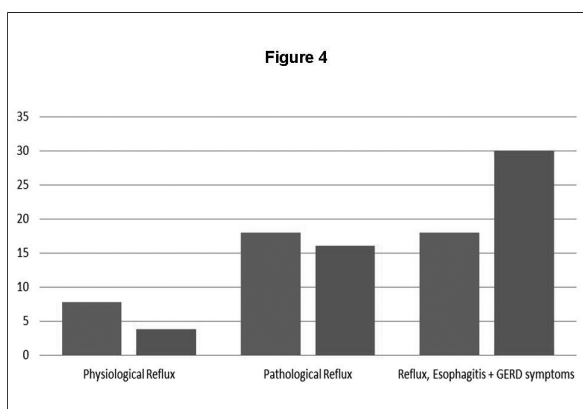
**Table 2:** Main drugs taken by elderly patients.

Disease	Age <65 y.o. (%)	Age >65 y.o. (%)
None	49.3	28.6
Cardiorespiratory	23.4	62.7
Vascular	8.7	18.9
Metabolic	16.1	21.5
Osteoarticular	27.9	45.8
Renal	14.5	24.5
Haepatic	19.6	27.3
Neuropsychiatric	6.2	18.4
Other	26.6	35.6

**Table 3:** GERD comorbidities

### Effects of aging on normal patterns of gastro-esophageal reflux

In a late study on 110 healthy subjects with a mean age of 38 years, an increase, though modest, of gastro-esophageal reflux in relation with age was seen, more common in women than in men. Furthermore, in older patients reflux was greater in supine position with various episodes longer than 5 minutes. However, the difference between groups of patients has not been proved significant, as more recently demonstrated by other authors. In elderly patients with symptomatic GERD, has been observed the existence of an higher acid reflux compared to younger patients, both in orthostatic or in supine position, to which also corresponds an higher frequency of severe esophagitis (Figure 4).



**Figure 4:** Reflux in patients with symptomatic GERD.

### Clinical manifestations

Heartburn and acid regurgitation are the symptoms commonly considered “typical” of GERD.

However, there is no symptoms complex that may be considered pathognomonic. Furthermore, GERD was properly represented as an iceberg, whose submerged part represents the majority of subjects with mild symptoms that rarely require therapy, while the emerging part corresponds to the smaller group of patients who, because of the severity of symptoms and/or lesions of esophageal mucosa, contact the physician and need a treatment<sup>(9)</sup>. In the study performed by Raiha et al. a group of 195 elderly patients subjected to gastrointestinal endoscopy for dyspeptic disorders, has been proved that 18% had grade II-IV esophagitis. Among these patients approximately half did not complain heartburn, unlike studies performed in younger ones in which this symptom was referred in 80% and 90% of cases. Moreover, heartburn was not correlated to the presence of GERD, unlike regurgitation, dysphagia and respiratory symptoms. Finally, a third of patients with esophagitis did not complain symptoms related to GERD<sup>(20)</sup>. In another study, however, heartburn was the predominant symptom among younger patients and elderly. In the latter, nevertheless, regurgitation and dysphagia were more frequent compared to the other group<sup>(52)</sup>. The absence of typical reflux symptoms could be explained by the presence of an autonomic neuropathy, which alters the severity and typology of symptoms, justifying the frequency of asymptomatic patients with complications such as stenosis, Barrett's esophagus and characteristic respiratory disorders of the elderly population affected by GERD such as asthma, chronic cough, recurrent pneumonia and interstitial pulmonary fibrosis<sup>(11,20,52,53)</sup>.

Among respiratory manifestations, asthma has been the most studied. The possible pathogenic mechanisms to be considered are the irritating action of gastro-esophageal reflux on the respiratory system or the presence of an esophageal-bronchial reflex vagus-mediated<sup>(19)</sup>.

Farther, studying the respiratory function in elderly patients with GERD using spirometry, it was proved that among these subjects with pathological pH-metric patterns, were present restrictive alterations. There are also frequent symptoms including hoarseness, chronic cough, chronic laryngitis, vocal cord granulomas or larynx cancer. Manometric studies have shown that LES pressure is reduced during the night, exposing pharynx to the damaging attack of gastro-esophageal reflux<sup>(16-18)</sup>.

Even dysphagia, characterized by the sensa-

tion of arrest or by a difficult progression of food along the esophagus, is a frequent symptom in elderly affected with GERD, also not complicated, in this case as an expression of a motility disorder, but may also be the predominant symptom of esophageal stenosis due to reflux or tumor. Regurgitation, symptom that typically occurs after meals, especially if in supine position, is the clinical expression of LES incontinence. In elderly this symptom is more common than heartburn which, however, can be associated with<sup>(11,54)</sup>.

## Complications

As already mentioned, the most frequent complications are represented by peptic stenosis and Barrett's esophagus. pH-manometric studies, in patients with Barrett's esophagus, have documented the presence of an excessive gastro-esophageal reflux, especially in supine position, a strict LES hypotonia and a reduced distal esophagus contractility. Diagnosis average age is around 60 years old, more frequently in males and smokers patients<sup>(7,8,55,56)</sup>.

There are no specific symptoms, and often patients have symptoms even mild or absent than those with esophagitis, probably due to a decreased acid-sensitivity of esophageal mucosa. There is now a general consensus in considering Barrett's esophagus a pre-neoplastic lesion, related to the onset of adenocarcinoma, which have a prevalence between 0.0% and 46.5% according to different series considered. Massive bleeding is rare, can be caused by ulcerative esophagitis and is usually triggered by precipitating factors such as antiplatelet agents and/or anticoagulants treatment. Conversely, microcytic-hypochromic anemia is found in about 5% of patients with esophagitis and, above all, may be the only clinical sign in elderly<sup>(9,21,57-59)</sup>.

## Diagnosis

GERD diagnosis is, usually, made by instrumental techniques; endoscopy and esophageal 24 hours pH-metry are the most used, because extremely sensitive and specific.

### *Esophagogastroduodenoscopy (EGDS)*

While in younger subjects aged around 50 years old, EGDS should not be considered a first-level exam and is only performed if a symptomatic

patient does not take advantage by a standard cycle of PPIs therapy, in elderly patients endoscopy must be considered a first-level exam, especially if there are alarm symptoms (e.g. weight loss, dysphagia, anemia, etc.). EGDS execution is necessary because symptomatology is often poorly represented and neoplastic diseases of esophagus and/or of gastric fundus, which initially may provoke symptoms similar to those of GERD, must be excluded<sup>(9,54,60-63)</sup>.

### *24h pH-metry*

Monitoring esophageal pH can be useful for GERD diagnosis and therapy, in particular for non-esophageal manifestations and non-cardiac chest pain. Is a valid method, fairly widespread, to quantify esophageal acid exposure. This measurement allowed to better understand the main characteristic of GERD pathogenesis and treatment. Calculate the percentage of total time spent below pH values of 4.0 in 24 hours (optimal discriminant value) and the association with symptoms is essential to evaluate atypical or sporadic disorders<sup>(53,64-67)</sup>.

### *Esophageal manometry*

Esophageal manometry purpose is to assess the cardia competence, to measure the mechanical properties of LES, to study esophageal motility and recording esophageal peristaltic activity, identifying primary and secondary motor disorders related to reflux. The stationary manometry, now disused, has been superseded by the ambulatory 24 hours registration, which records the motility of esophageal body, allowing the study of circadian motor events and their correlation to physical activity, meals and sleep<sup>(16-18)</sup>.

### *Gastric scintigraphy*

It has become the gold standard for the study of gastric emptying. It is minimally invasive, well accepted and with minimum radiation amount. However, it is not quite common or standardized. The lack of standardization and the probable heterogeneity of populations studied, justify the different results reported by literature, although the majority of studies seems to show a slow emptying in the elderly<sup>(19,68,69)</sup>.

## Treatment

GERD management in elderly patient should consider some variables common among this patients such as:

1) the presence of comorbidity that requires specific therapies and create the problem of interactions with drugs commonly used in GERD;

2) the possible reduction in compliance, for physical or psychiatric disorders, as well as for the possible complexity of dosages, reducing the effectiveness of treatment;

3) the changes in drug detoxification related to age<sup>(2,70)</sup>.

Is important to remember that clinical studies for the GERD evaluation, generally, are carried out on a younger population. The therapeutic approaches commonly used in clinical practice are, initially, a non-pharmacological measures, or rather hygienic-dietary-behavioral, such as body weight reduction, smoking cessation (it has been proved that smoke reduces LES tone), elevation of the headboard, abolition of certain foods and drugs and, finally, in a few non-responders patients a surgical intervention<sup>(2-4)</sup>.

Treatment goals are, in the attack phase, symptoms resolution and healing of injuries resulting from changes in lifestyle, not always effective and practicable, and from drug therapy. Another objective is to consolidate the results obtained maintaining remission of symptoms, healing of injuries, and also preventing the complications<sup>(71)</sup>.

Since the gastric acid reflux is one of the most important factors in GERD pathogenesis, the control of acid secretion is the primary objective in this area and several controlled clinical studies have demonstrated the greater efficacy of PPIs compared with H2 antagonists, drugs whose use is now limited to only those few patients who cannot tolerate PPIs, or in association with the same PPI in poorly responsive cases<sup>(2-4)</sup>.

Other medications used are antacids, capable of a temporary effect against acid secretion and prokinetics, which allow to improve the esophageal clearing, gastric emptying and increase the basal tone of LES. When the disease is frequently relapsing, resistant to medical therapy and/or complicated (severe esophagitis and/or stenosis), should be considered the surgical approach, although, because of the surgical risk of elderly patients, is rarely practiced, even with the most modern and less invasive laparoscopic techniques<sup>(2-4)</sup>.

## Medical therapy

Choosing the drug in geriatric patients is based on the assessments of:

- effectiveness;
- tolerability and drug interactions;
- pharmacokinetic characteristics<sup>(2,70)</sup>.

Antacids and mucus-protective

Antacids and mucous-protectors, such as sucralfate and alginic acid, are usually taken as self-medication before consulting the doctor, or prescribed by a general practitioner if symptoms are mild. In addition, they are sometimes used in combination with other drugs classes, in particular prokinetics. In literature, there are some comparative studies between alginate-antacids and placebo, which show a limited role in controlling symptoms for alginic acid<sup>(2-4,70,72)</sup>.

## H2-antagonists

As already said, in the therapy of esophagitis a prominent role is played by drugs that reduce gastric acid secretion<sup>(73,74)</sup>. H2-antagonists have determined, in the '70s, a breakthrough in the treatment of this disease, demonstrating a good effect both on the improvement of symptoms and on the healing of injuries, but with limited efficacy at standard doses (used in peptic ulcer) as the healing rates were not higher than 50%. Recent studies show that only higher doses (1200-2400 mg) of H2-antagonists allow to improve the healing rate which, however, is less consistent than their effect on the symptoms.

Nevertheless, the administration of H2-antagonists in the elderly may cause various dose-dependent side effects. The most important is central nervous system involvement with a variety of symptoms, including: delirium, confusion, hallucinations, depression, decreased libido and Parkinsonism. The incidence of these effects increases particularly in patients with renal failure, so these medicaments should be abandoned<sup>(2,3)</sup>.

## Proton Pump Inhibitors

Drugs that block the proton pump are certainly the most effective in the GERD treatment; they determine a marked and prolonged reduction of gastric acidity and, consequently, reduce reflux<sup>(75-78)</sup>.

The use of these molecules has also allowed the healing of H2-antagonists refractory esophagi-

tis. Historically, the first PPI introduced in clinical practice was omeprazole, to which was subsequently added lansoprazole and pantoprazole, with an almost equivalent effectiveness<sup>(79)</sup>.

Although effectiveness of the various PPIs is comparable, it seems appropriate to emphasize the characteristics of pantoprazole and rabeprazole<sup>(80)</sup>. These molecules, in fact, besides having a more rapid activation in a strongly acid pH and, probably, a greater selectivity for the acid compartment of the gastric parietal cell, are especially characterized by a less interaction with the hepatic oxidative enzyme systems, connected to cytochrome P450, which make them more manageable, and secure specially in elderly patients or in those with decreased hepatic and renal function, without adjusting the dose and, above all, with a lower risk of drug interactions<sup>(81)</sup>.

James et al. conducted a clinical trial comparing H<sub>2</sub>-antagonists and omeprazole in elderly patients with esophagitis. In these patients, omeprazole was approximately three times more effective than H<sub>2</sub>-blockers (68% vs. 23%) on healing and symptom resolution, even more than in younger patients (57% vs. 29%)<sup>(82)</sup>.

The last molecule of PPIs group, esomeprazole, isomeric omeprazole derivative, showed a more powerful anti-secretory action with daily doses of 40 mg, which produced a significant benefit in the treatment of erosive esophagitis and in pain chest, with healing rates slightly higher than with other PPIs<sup>(2,83)</sup>.

### **Prokinetic**

Also these drugs are useful in GERD treatment, considering the motor pathogenesis of this disease. In fact, these molecules carry out their action on esophagus, LES and stomach, increasing contraction force (effect of esophageal clearing), enhancing LES tone (improving the skills of the anti-reflux barrier) and accelerating gastric emptying. The molecules most frequently used are domperidone (anti-dopaminergic action), metoclopramide (central dopaminergic antagonist), and levosulpiride, which due to the several side effects has limited use. GERD natural history shows that up to 80% of patients have a relapse after acute healing, usually within six months from treatment interruption. This determines the need for a long-term therapy<sup>(28,84)</sup>.

### **Step-up and step-down therapy**

Recently there has been many discussion about the role of the molecules which should be used in patients with suspected GERD and what should be the most cost-effective approach. The therapy can be started immediately using the more effective molecules, then lowering the dosage or switching to a less strong drug (step-down), sufficient to control the symptoms; or start with those less powerful and, in case of failure, continue with more powerful ones, to obtain the disappearance of symptoms (step-up). Both strategies have pros and cons, but there is no doubt that the higher cost of more effective drugs (PPIs), is quickly offset by better results both on symptoms and on wound healing<sup>(2,83)</sup>.

### **Surgical therapy**

Is the alternative to medical therapy. The indications for GERD surgical treatment are very limited and are represented by medical therapy failure and esophagitis development, complications such as ulcers, stenosis and recurrent episodes of bronchial aspiration occurrence<sup>(58,81,85,86)</sup>.

In absence of complications surgery is a viable option if symptomatology interferes significantly on the patient quality of life and if the latter refuses a long term medical therapy. The mere presence of hiatal sliding hernia is not an indication for surgery. A randomized clinical trial has demonstrated the greater efficacy of surgery (Nissen fundoplication) compared to medical therapy with PPIs in male patients with complicated GERD<sup>(87,88)</sup>.

However, the indications for surgery are generally limited to young patients with a life expectancy of many years, in which precisely surgical therapy can be an effective alternative to medical one. The recent introduction of laparoscopic surgery in GERD treatment, has expanded the number of subjects on which can be carried out the intervention of Nissen fundoplication<sup>(58,89)</sup>.

The short-medium term clinical results are comparable to those produced by traditional surgery. Lately, 359 patients aged > 65 years study showed, after the intervention, a similar symptoms improvement to that found among younger patients, an equivalent morbidity and length of hospitalization, emphasizing that the choice of surgical treatment is no longer limited by age. Nevertheless we must consider that elderly patients have a higher surgical risk than younger ones<sup>(2,90,91)</sup>.



### Endoscopic therapy

Medical and surgical therapy are undoubtedly two cornerstones of GERD treatment, but to date endoscopy offers new possibilities<sup>(92,93)</sup>.

Three different approaches are available today:

1) using an endoscope “sewing machine”. With this technique could be performed sutures within the cardia to form mucosal folds that contrast reflux<sup>(94,95)</sup>;

2) trough Radio-Frequency (NARROW procedures), producing focal lesion in the cardia muscle layer that hesitate in fibrosis with reflux reduction<sup>(95,96)</sup>;

3) injection of inert substances (polymers) into the esophageal-gastric junction determines the creation of an anti-reflux barrier<sup>(95,97)</sup>.

These procedures seem very promising, but unfortunately are just in an experimental stage. Before being widely adopted will be necessary to make more accurate studies and a better standardization of procedures<sup>(95,98)</sup>.

### Conclusions

In conclusion, GERD is a common condition in the elderly, which often develops itself in an atypical way, with more frequent and severe complications. As regards the pathophysiological mechanisms in elderly patients compared to younger ones, seem to have a specific role factors such as use of drugs that reduce the LES tone or have direct detrimental action on the esophageal mucosa (in this regard a special note, in women, the use of osteoporosis medications, especially bisphosphonates, for the well-known esophageal lesions that can cause), presence of comorbidities (diabetes mellitus, neurological disorders), hiatal hernia, overweight, being bedridden and probably duodenal-gastric reflux. While the progressive age-related decrease of hydrochloric acid (HCl) secretion, does not seem to have an important protective role.

The diagnostic and therapeutic approach must consider the psychological and physical changes often present in the elderly. In absolute terms, treatment effectiveness is very similar between young and elderly. PPIs in the elderly, as in the young, are considered the most effective molecules on symptoms and lesions of all grades. The choice of a specific molecule between PPIs has no influence in the young, while in the elderly is required accounting

comorbidities and polypharmacy (interactions).

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