gastrointestinal disorders

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Review

Main Disorders of Gastrointestinal Tract in Older People: An Overview

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Abstract: From a physiological standpoint, aging is a progressive reduction in each organ system's capacity to maintain homeostasis in the face of illness or stressors. With advancing age, gastrointestinal (GI) symptoms and signs may increase, not only due to the aging processes but also to the superimposed effects of comorbidities, which can badly affect digestive functions (i.e., diabetes, malignancy, etc.) and environmental exposure. In general, gastrointestinal symptoms in older people more often underlie organic pathologies, while GI functional disorders are less frequently diagnosed in this age group. Moreover, gastrointestinal disease can also present in a nuanced and atypical manner, making the diagnostic hypothesis and, consequently, the correct diagnosis and therapy more challenging. In addition, with reference to this age group, the clinical implications of gastrointestinal pathologies can be more severe due to a decreased physiologic reserve, with a higher risk for malnutrition resulting in falls, depression, social isolation, and a deterioration of functional status. In this review, we focused on the most frequent GI tract disorders, highlighting the main age-related changes, their epidemiological, pathophysiological and clinical implications, and any differences with younger patients.

Keywords: gastrointestinal diseases; elderly; aging; functional; organic

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1. Introduction

Advancing age is responsible for a well-known progressive reduction in each organ system's capacity to maintain homeostasis in the face of illness or stressors [1–3]. In most countries, average life expectancy commonly exceeds 80 years, leading to an increase in the effort to obtain a deeper global consciousness about age-related diseases and their related burden on health systems. Several conditions commonly affect older people, such as cardiovascular disease, diabetes mellitus, dementia, etc. Regarding the gastrointestinal (GI) system, aging may affect both the gastrointestinal tract and the accessory glandular organs (i.e., liver, gallbladder, and pancreas) by deteriorating digestion and absorption functions. Moreover, besides the aging processes, the concomitant effects of comorbidities, such as the alteration of intestinal motility by diabetes mellitus, may, in turn, badly affect the digestive functions [3,4]. Whether it is impossible to make a categorical division, usually GI symptoms in older people underlie organic pathologies, while GI functional disorders are less frequent in this age group. Although there are no specific GI diseases limited only to older age, some GI conditions can manifest in a nuanced and atypical manner, making the diagnostic hypothesis and, consequently, the correct management more challenging. In addition, the clinical implications of GI pathologies can be more severe with advancing age due to a decreased physiologic reserve and a consequent higher risk for malnutrition, resulting in falls, depression, social isolation, and a deterioration of functional status.

2. Aim

The aging process may significantly impact GI system functions. In this review, we chose to focus on the most frequent GI tract disorders, highlighting the main age-related changes, their epidemiological, pathophysiological and clinical implications, and the eventual differences with younger patients.

3. Basic Mechanisms of Aging Gastrointestinal Tract

Aging is associated with structural and functional alterations in the GI system due to different pathogenic mechanisms, as shown in Figure 1 [1–3]. These modifications affect gut motility, as well as intestinal absorption and intestinal immune functions. Although aging per se appears to have a minor effect on GI function, aging-related physiological alterations could become relevant when a superimposed stressor occurs, mainly since there is an overall reduced functional reserve with advancing age [4] (Figure 1).

Main pathogenic mechanisms involved in age-related changes in gastrointestinal system	
Neurological (central)	- Impairment in cognitive functions - Impairment in swallowing mechanisms
Neurological (peripheral)	- Impaired esophageal peristalsis - Disturbance in function of lower esophageal sphincter - Slowing of gastric emptying - Increased colonic transit time
Metabolic	- Impaired glucose, lipid and bile acid metabolism - Electrolyte disorders
Immunological	- Imbalance between anti-inflammatory and pro-inflammatory cytokines - Impairment of innate immune system
Microbiome-related	- Alterations in composition, diversity and functional features of intestinal microbiota
Drug-induced	- Mucosal injury - Impaired motility - Dysregulation of immune and microbiome homeostasis
Aging-related frailty	- Age-related decline in physiological function and adaptive capacity

Figure 1. Main pathogenic mechanisms involved in age-related changes in GI system.

Aging is associated with motility changes at different levels of the gastrointestinal tract. Impaired esophageal peristalsis, disturbance in the function of the lower esophageal sphincter [5], slowing of gastric emptying [6], and increased colonic transit time [7] have been described in healthy asymptomatic old adults. In contrast, the majority of studies indicate that the motility of the small bowel does not change with age [8,9]. The modest slowing of gastric emptying described in healthy aging impairs appetite regulation and could favor the development of the so-called anorexia of aging, which leads to consequent weight loss and sarcopenia. On the same note, changes in structure, physiology, and innervation of the swallowing system occurring with healthy aging [10,11], collectively called presbyphagia, are predisposed to the development of dysphagia when superimposed stressor occurs (i.e., delirium, dementia, and adverse effect of medication or hospitalization).

Moreover, degeneration of the myenteric plexus fibers and neurons has been described with aging [12,13]. This mechanism could play a pivotal role not only in the genesis of motility disorders [1] but also in the impairment of intestinal absorption. Animal models showed degeneration of the myenteric plexus, consequent degeneration of the villi, and reduction in secretory function [14], as well as mucosal atrophy and altered epithelial tight junction structures, occurring with advancing age [14]. These alterations could increase intestinal permeability and lead to persistent immune activation [15].

Finally, aging is associated with structural and functional mucosal defense defects, such as a decrease in the cytoprotective mucus-bicarbonate barrier, reduction in gastric blood flow, and impaired repair mechanisms [16]. These findings collectively weaken gastric defenses and can reduce tolerability to certain medications (i.e., NSAIDs), mainly in the oldest categories.

The gut-associated lymphoid tissue (GALT) is the largest immunologic organ, and it is part of the gastrointestinal tract defense system, along with the mucosal layer, the biochemical defense (pH and enzymes), and the microbiota [15,17]. Immunosenescense appears to arise in the mucosal immune system of the GI tract earlier than in systemic immune compartments and leads to reduced response against pathogens. Changes in mucosal immune function may be related to the imbalance between anti-inflammatory and pro-inflammatory cytokines, with increased production of the latter, such as IL-1b, IL-6, and TNFa [15]. The resulting chronic low-grade inflammation is associated with frailty and increased morbidity and mortality [18]. Overall, impairment of the innate immune system, together with an age-related decrease in acid secretion [19] and aging of the mucosal surface, which made them more susceptible to injury [20], contribute to an increased incidence and severity of infections in older individuals.

4. Main Gastrointestinal Tract Disorders in Older People

The review is based on a literature search of PubMed, Web of Science, and Embase databases up to November 2023. The following MeSH terms or keywords were used: "gastrointestinal diseases and older people", "gut disorders and older people", and "aging gut". We included the most relevant reviews and extensive works on this field, mainly focused on specific clinical manifestations and management in the elderly. Case reports were not eligible for inclusion. In consideration of the heterogeneity of studies available for each of the covered conditions, we selected papers highlighting the most relevant and current findings. In most of the studies we reviewed, the cut-off used to identify older adults is represented by age > 65 years old. When different cut-offs were considered, they were indicated in the text.

Figure 2 summarizes the main GI tract disorders in older people, divided according to upper GI tract, small bowel, and lower GI tract involvement.

Main gastrointestinal tract disorders in older people	

Upper gastrointestinal tract	- Dysphagia
	  - Oropharyngeal dysphagia
	  - Esophageal dysphagia
	- Functional dyspepsia
	- Gastro-esophageal reflux disease
	- Helicobacter pylori related-conditions
	- Chronic atrophic gastritis
	- Peptic disease
	- Gastric cancer

Small bowel	- Celiac disease - Mesenteric ischemia - Small intestinal bacterial overgrowth
Lower gastrointestinal tract	- Diverticular disease - Inflammatory bowel disease - Microscopic colitis - Irritable bowel syndrome - Infections - Drug-induced diarrhea - Colon-rectal cancer - Constipation and incontinence

Figure 2. Main gastrointestinal tract disorders in older people.

4.1. Upper Gastrointestinal Tract Diseases

4.1.1. Dysphagia

Dysphagia, defined as an impairment of the swallowing process, is a remarkably common disorder in the older population, with a significant impact on the quality of life and the consumption of healthcare resources. It is estimated that about 15% to 40% of the population aged over 65 is affected by dysphagia, with a higher prevalence (up to 60%) in nursing home settings [21,22]. It is a relevant clinical problem whose consequences can range from dehydration and malnutrition to silent or overt aspirations that result in pneumonia and exacerbation of chronic lung diseases [11,23], with consequent increased rates of mortality and long-term care admission. The reasons for the higher incidence and severity of dysphagia in the elderly take place not only in the increased burden of age-related diseases affecting the swallowing muscles but also in changes in structure, physiology, and innervation of the swallowing system occurring with healthy aging [10,11]. These alterations, so-called presbyphagia, are predisposed to the development of dysphagia when a superimposed stressor occurs (i.e., delirium, dementia, adverse effect of medication, or hospitalization) [11,24,25]. However, in clinical practice, dysphagia should never be attributed to the normal aging process without an appropriate diagnostic work up. Indeed, it is important to underline that dysphagia in the elderly represents an alarm symptom, especially if associated with signs suggestive of malignancy, such as sudden weight loss, dysgeusia or anemia, and a history of smoking and alcohol abuse. These symptoms should raise concern for neoplasms of both the oropharyngeal and gastroesophageal tract.

Two major types of dysphagia are recognized: oropharyngeal and esophageal dysphagia. In particular, oropharyngeal dysphagia is a commonly recognized neurological (stroke and motor neuron diseases) cause while esophageal dysphagia is commonly recognized as structural (Zenker diverticulum, esophageal ring, Schatzky rings, and head and neck cancer) or functional (achalasia, gastroesophageal reflux disease, eosinophilic esophagitis, infections, and ingestion of caustics) causes [26].

At present day, there is still a lack of guidelines for the management of dysphagia in older adults. It requires a multidisciplinary approach with attention to balancing functional and, more importantly, nutritional status, which are vital determinants of health outcomes.

Presbyesophagus should be considered when other organic differential causes of dysphagia have been excluded. It refers to the age-related changes in the esophagus, including decreased lower esophageal sphincter relaxation, upward displacement of the lower esophageal sphincter into the intrathoracic position, and delayed emptying of the esophagus in association with repetitive nonperistaltic (sometimes called "tertiary") esophageal contractions [27]. Adverse effects of aging on the swallowing process are likely to contribute to the increased reports of choking spells and aspiration [28]. From a histological point of view, presbyesophagus is characterized by a reduction in myenteric ganglion cells, thickening of the smooth muscle layer, and a lymphocytic infiltrate of the myenteric plexus. However, the clinical significance of these changes remains uncertain because most individuals appear well compensated and clinically unaffected [29].

4.1.2. Functional Dyspepsia

The term dyspepsia identifies a set of symptoms referable to the upper gastrointestinal tract, including abdominal pain or discomfort, postprandial fullness, abdominal bloating, belching, and early satiety. From an etiological viewpoint, there are two major forms of dyspepsia: secondary dyspepsia with organic, systemic, or metabolic causes for symptoms identified by specific investigations (including *Helicobacter pylori* dyspepsia) and functional dyspepsia [30]. According to Rome IV criteria, functional dyspepsia is defined by one or more of the following symptoms: postprandial fullness, early satiation, epigastric pain, and epigastric burning occurring at least 1 day per week in the past 3 months with at least a 6-month history [31]. It encompasses two clinical syndromes, postprandial distress syndrome (PDS), characterized by meal-induced dyspeptic symptoms, and epigastric pain syndrome (EPS), which does not occur exclusively postprandially [32]. The prevalence estimated for

dyspepsia in the elderly ranges from 9% to 25% [33], although recent studies have shown that dyspepsia prevalence declines to some extent in the over-60 age group [34,35].

When approaching older patients complaining of dyspeptic symptoms, prompt investigation may be more appropriate than empirical treatment because of the higher proportion of patients with organic diseases mimicking functional dyspepsia and the likelihood of malignancy [36]. Indeed, guidelines recommend upper gastrointestinal endoscopy as a frontline approach in patients aged over 60 years unless they are too frail, possibly with gastric and duodenal biopsy, to rule out cancer and peptic ulcer [37]. Management of functional dyspepsia includes making a secure diagnosis, treatment with proton pump inhibitors (PPI) in EPS, careful choice of prokinetics in PDS, and, eventually, the use of tricyclic antidepressants [32].

4.1.3. Gastroesophageal Reflux Disease

Among all causes of dyspepsia, gastroesophageal reflux disease (GERD) represents one of the most relevant, in consideration of its high prevalence, in the elderly [38]. A study by Moore et al. conducted on 20,000 nursing home residents aged over 65 years showed that the prevalence of GERD is about 23% [39]. However, symptoms of GERD in the elderly are often mild and atypical, including dysphagia and respiratory symptoms (cough, wheezing, and hoarseness), making GERD diagnosis often overlooked and the disease undertreated in this age category. Furthermore, in the face of fewer symptoms, the disease is more severe with higher esophageal and extraesophageal complication rates (such as erosive esophagitis, esophageal stricture, Barrett's esophagus, and adenocarcinoma of the esophagus) with potentially life-threatening consequences [38,40,41]. Diagnostic work up and treatment are similar to the general population: Empiric therapy with PPIs, together with dietary and behavioral measures, is the first-line therapy when GERD is suspected. Endoscopy should always be performed in the presence of alarm symptoms or additional risk factors for Barrett's esophagus. Regarding laparoscopic anti-reflux surgery, older age per se is not a contraindication, as shown in a study by Fei et al. [42], and should be considered in a selected group of patients.

4.1.4. *Helicobacter pylori*

Helicobacter pylori (*H. pylori*) infection is a relevant clinical problem, as approximately 50% of the world population is estimated to be infected with this pathogen [43]. The infection is usually acquired during childhood and is mostly related to socioeconomic status and living conditions early in life. From an epidemiological point of view, *H. pylori* prevalence is falling worldwide, especially in industrialized countries [44], but the prevalence and severity of this infection remain higher in the elderly than in the younger ones, especially in nursing home settings [45,46]. Moreover, eradication failure is more common among older people, given the high prevalence of antibiotic resistance compared to younger subjects [47]. This explains why this infection, left untreated, leads more frequently to the development of gastric and nongastric pathologies in this subgroup of patients. In particular, *H. pylori* infection is associated with greater bleeding risk, especially in the presence of other risk factors, such as concomitant use of NSAIDs [48]. Although current guidelines suggest testing and treating *H. pylori* in all patients over the age of 60 presenting with dyspepsia [49], they overlook the management of *H. pylori* in the elderly. Moreover, it is not uncommon for reluctance among clinicians to treat patients with advanced age because of concern about adverse side effects. A recent study conducted by Kobayashi et al. showed that triple therapy for *H. pylori* (containing a PPI and two antibiotics) is safe and effective without an increased frequency of adverse events among the elderly (aged 65–74) and super-elderly (aged over 75) groups [50]. However, based on the available literature data, given its superiority, bismuth quadruple therapy may be considered the empirical and preferable treatment regimen for *H. pylori* eradication in the elderly [51] if antibiotic susceptibility testing against *H. pylori* has not been performed. The high eradication rate

with this treatment regimen reduces the need to resort to further lines of treatment in case of failure [52].

4.1.5. Chronic Atrophic Gastritis

Chronic atrophic gastritis (CAG) is identified by the replacement of appropriate gastric glandular structures with connective tissue (not metaplastic atrophy) or a different, non-native epithelium (metaplastic atrophy) on a background of chronic inflammation [53]. It is generally related to either *H. pylori* infection or autoimmunity. This condition is typically asymptomatic and may go undiagnosed or may present with nonspecific gastric and extragastric manifestations that may occur later in the course. Regarding older people, the prevalence of CAG is quite high, with rates ranging from 50% to 70% in those above 60 years [54,55], and the most prevalent form is the seronegative one related to *H. pylori* infection [53]. Advanced age is not an independent risk factor for CAG, as previously thought, but current data suggest that the higher prevalence of CAG in elderly people is related to the higher prevalence of *H. pylori* infection in this age group, as previously discussed [54]. No data are available about specific symptoms in the elderly. In any case, the decrease in acid secretion occurring as a consequence of chronic atrophic gastritis leads to bacterial proliferation in the small intestine (SIBO) and malabsorption of nutrients, such as vitamin B12 [56], might be more relevant with advancing age, mainly if associated with other nutritional deficits. Moreover, CAG represents a preneoplastic condition that can lead to the development of gastric carcinoma. Indeed, surveillance is indicated in a selected group of patients [53]. Treatment depends on the etiology; in particular, eradication of *H. pylori* infection is associated with a decrease in gastric activity and prevention of progression of intestinal metaplasia [57,58].

4.1.6. Peptic Disease

Peptic ulcer disease (PUD) is characterized by discontinuation in the inner lining of the gastrointestinal tract (most frequently of the stomach and duodenum) because of an imbalance between gastric mucosal protective and destructive factors [59]. The most important risk factors for the development of PUD are *Helicobacter pylori* infection and the use of NSAIDs. While epidemiological studies report that the incidence of peptic disease is decreasing in the general population, the rate of hospitalization and mortality for gastric and duodenal ulcers remains high in old patients [60]. This is mainly due, firstly, to the higher prevalence of *H. pylori* infection and prescription of NSAIDs in this age group, but also to the presence of comorbidity and multidrug therapy (such as anti-thrombotic drugs and bisphosphonates). It is well documented the association between antiplatelet therapy (i.e., low-dose aspirin) and dyspepsia, as well as the risk of ulcer and GI bleeding in patients aged over 70 years [61]. This is ascribable to the aging-related increased susceptibility of the gastric mucosa to injury, in particular when antiplatelet therapy is associated with other noxious agents such as NSAIDs, alcohol consumption, and *H. pylori* infection [62]. Moreover, the age-related reduction in the gastric and duodenal mucosal barrier function, resulting from decreased mucosal blood flow, gastric mucus, bicarbonate secretion, or cell proliferation, plays a key role in the increasing incidence of these *H. pylori*-negative ulcers in the elderly [60]. Clinical presentation of peptic disease in these subjects is often atypical, resulting in diagnostic delay and increased development of complications. As for younger subjects, treatment involves the eradication of *H. pylori* infection, if present, and the use of anti-secretory drugs such as pomp proton inhibitors (PPIs) and, in case of bleeding ulcers, resuscitation and endoscopy procedures.

4.1.7. Gastric Cancer

Gastric cancer can be considered an age-related disease, with a peak incidence occurring in the seventh decade of life. Different works showed that gastric cancer in the elderly exhibits peculiar clinical and pathological features. A study comparing characteristics and prognosis of this cancer among different age subgroups showed that gastric cancer in patients aged > 70 years is more frequently located in the upper third of the stomach, well differentiated, with larger tumor size and more advanced tumor–node–metastasis stage, but less distant metastasis in comparison to younger categories [63]. Moreover, older patients display poorer overall survival [63]. Current guidelines for the management of gastric cancer are predominantly based on evidence from clinical trials performed in younger and fit patients. Patients with operable gastric cancer should undergo surgical resection, preferring subtotal gastrectomy in the elderly because of the higher rates of postoperative morbidity and mortality of total gastrectomy in this subgroup [64,65]. In inoperable cancer, chemotherapy can be considered, taking into account the functional status and comorbidity of each patient. A recent randomized trial demonstrated that in old (median age 76 years old) and frail 514 patients with gastroesophageal cancer, a lower dose of chemotherapy does not compromise disease control or survival and provides a better quality of life [66].

The main take-home messages relative to the abovementioned upper gastrointestinal tract conditions in older people are summarized in Figure 3.

More common upper gastrointestinal tract conditions in older people - Main take-home messages -	
Dysphagia	- Avoid attributing it to the aging process - Consider appropriate diagnostic work up to exclude malignancy
Dyspepsia	- Higher proportion of old adults have organic causes, so prompt investigation may be more appropriate than empirical treatment
GERD	- Diagnostic work-up similar to the general population
***H.pylori* related-conditions**	- It is useful to test and treat all the infected patients - Bismuth quadruple therapy may be the preferred regimen with a high eradication rate reducing the possibility of further lines of treatment in case of failure
Chronic atrophic gastritis	- Rarely associated with an autoimmune condition in the elderly - In global population, it may represent a preneoplastic condition
Peptic disease	- Atypical clinical presentation in older adults may cause diagnostic delays and increased complications
Gastric cancer	- It is considered an age-related disease - When indicated, subtotal gastrectomy and low dose chemotherapy are preferred

Figure 3. Main take-home messages relative to more common upper gastrointestinal conditions in older people. Abbreviations: GERD = gastroesophageal reflux disease.

4.2. Small Bowel Diseases

4.2.1. Celiac Disease

Celiac disease is an autoimmune chronic enteropathy that occurs in genetically predisposed individuals following gluten intake and typically presents with a malabsorption syndrome (chronic diarrhea, micronutrient deficiency, and weight loss). Once considered a children's disease, there is currently growing evidence of an increased diagnosis in the elderly (aged over 65), especially in men [67], not only because of diagnostic delay but also as a new-onset disease in patients with long-lasting tolerance to gluten in the past [68]. As for other gastrointestinal disorders, celiac disease in the elderly often presents in a mild and nuanced matter (abdominal bloating, flatulence, and abdominal discomfort) [69] with consequential diagnostic delay and increased morbidity in this age group. The first

and sometimes only signs and symptoms of the disease can be related to micronutrient deficiency [69]. In fact, 60–80% of older patients with celiac disease have anemia generally related to iron deficiency or, less frequently, of acid folic and/or vitamin B_{12}, which can raise the suspicion of a neoplastic pathology [67]. Celiac disease can also cause deficiencies in the absorption of vitamin D and calcium, leading to a possible depletion of bone mass, already weakened in most of the elderly because of other causes, and hypoalbuminemia, resulting in the development of edemas and ascites. In some patients with celiac disease, hepatocellular changes may also occur, a condition called celiac hepatitis, and it is characterized by abnormal liver function tests [70]. Some autoimmune diseases are frequently associated with celiac disease, such as autoimmune thyroid disorders and type 1 diabetes mellitus [71]. Their presence, together with the detection of intestinal symptoms, even if mild and/or micronutrient deficiencies, may strengthen the suspicion of celiac disease. The diagnostic work up of celiac disease in the elderly follows the same guidelines valid for younger patients. A gluten-free diet is the cornerstone of the treatment, which, however effective, may be limited by lower adherence in this population since there is difficulty in changing eating habits and finding such products in homes. Moreover, refractory celiac disease, characterized by the presence of a severe enteropathy with significant malabsorption, not responsive to the gluten-free diet, occurs more frequently in the elderly than in young people [72]. The most common cause of this complication lies in the contamination of the diet by gluten, also in the form of a pharmacological excipient. Some complications of celiac disease may be particularly problematic for the elderly, such as neurological complications (ataxia and neuropathy), which may lead to an increased risk of falls and bone metabolism complications, resulting in an increased risk of fractures. Older patients have also an increased risk of developing intestinal lymphoma, non-Hodgkin lymphomas, and adenocarcinomas of the gastrointestinal tract [67]. The incidence of intestinal lymphoma increases after the sixth decade of life and is more common in patients diagnosed with celiac disease between the ages of 50 and 80; it presents with multifocal ulcerated lesions and can become complicated with intestinal perforation [73].

4.2.2. Mesenteric Ischemia

Mesenteric ischemia is a rare disease, mainly affecting older subjects, and linked to an inadequate blood flow to the intestinal tract able to support metabolic needs. Based on the time of onset, it can be classified as acute or chronic.

Acute mesenteric ischemia (AMI) is a sudden interruption of blood supply to the intestine, mainly caused by mesenteric arterial embolism (50%), mesenteric arterial thrombosis (15–25%), or mesenteric venous thrombosis [74], that leads to cellular damage and intestinal necrosis. It is an underestimated cause of acute abdomen in the elderly, with an incidence that increases exponentially with age, particularly in patients aged over 75 years [75], and a mortality rate ranging from 60 to 80% of affected patients, especially in case of diagnostic delay. AMI should always be suspected in elderly patients with cardiovascular and atherosclerotic risk factors, presenting with severe abdominal pain 'out of proportion to the physical examination', vomiting, bloody stools, and diarrhea. However, in patients who develop AMI upon atherosclerotic disease (acute or chronic), the clinical picture could be vague, with mild abdominal pain, vomiting, and diarrhea [76]. A delayed diagnosis due to a clinical presentation with nuanced symptoms and the presence of comorbidity may contribute to high mortality. Clinical suspicion guides the diagnosis, and it is a major factor in the correct interpretation of computed tomography (CT), which is the diagnostic gold standard. Treatment depends on the etiology, either endovascular treatment for AMI caused by an arterial embolism or arterial thrombosis or systemic anticoagulation in mesenteric venous thrombosis. For AMI caused by nonocclusive ischemia, treatment is based on improving perfusion and correcting the cause of hypoperfusion. Immediate surgery can be considered in emergency conditions when there are signs of peritonitis and bowel necrosis.

Chronic mesenteric ischemia (CMI) is caused by the stenosis or occlusion of at least one of the visceral arteries and occurs predominantly in older women suffering from atherosclerosis and with a history of smoking [77]. Chronic mesenteric ischemia is associated with the presence of cardiovascular risk factors such as hypertension, diabetes mellitus, and dyslipidemia, and the presence of ischemic heart disease, carotid atherosclerosis, history of stroke, and chronic kidney disease [77]. Symptoms associated with CMI are often nonspecific, such as weight loss, postprandial abdominal pain (abdominal angina), food avoidance, early satiety, nausea, vomiting, and diarrhea/bloating after eating. These symptoms can often direct the clinician towards a suspicion of malignancy, leading to a diagnostic delay. The diagnosis of CMI is clinical and is based on the analysis of the symptoms reported by the patient and CT angiography. All patients with symptoms should undergo revascularization. Endovascular therapy is widely preferred over open revascularization because of its associated lower morbidity and mortality rates after treatment [78].

4.2.3. Small Intestinal Bacterial Overgrowth

The gut contains a high number of bacterial cells performing different functions for the host. Their concentration increases progressively along the gastrointestinal tract, reaching about 70% in the colon. The composition of the bacterial species also varies by site. In the small intestine, there are mainly Gram-positive and aerobic bacteria, while in the large intestine, there are predominantly Gram-negative and anaerobic. Small intestinal bacterial overgrowth (SIBO) is defined when an upper gut aspirate detects 10^5 or more colony-forming units per mL [79]. However, even though gut aspirate is the gold standard, the most used diagnostic test currently is the noninvasive glucose breath test. Clinically, SIBO should be suspected in the presence of chronic diarrhea, malabsorption, weight loss, bloating, meteorism, and secondary nutritional deficiencies. The prevalence of SIBO increases progressively with age. A study by Parlesak et al. demonstrated that the prevalence of SIBO in the healthy population is significantly higher among patients aged 61 and older when compared to younger adults [56]. Older people may be more susceptible to SIBO than their younger counterparts as a result of reduced gastric secretion (due to a larger use of PPIs), reduced GI motility, intestinal surgery, and small bowel diverticulosis [56], with a subtler clinical presentation, characterized by nonspecific abdominal distention, bloating, and poorly localized discomfort that may mimic other diseases. Signs and symptoms of nutritional deficiencies, such as a deficit of vitamin B12, might be the first signs in the elderly [79]. Treatment includes dietary changes emphasizing a low carbohydrate diet, increasing GI motility by use of prokinetic agents, and reduction in bacterial overgrowth using nonabsorbable antibiotics.

The main take-home messages relative to the abovementioned small bowel conditions in older people are summarized in Figure 4.

More common small bowel conditions in older people - Main take-home messages -	
Celiac disease	- Same work up and treatment as younger patients - Increased risk of complications in older patients - Growing incidence of new-onset disease in older people
Mesenteric ischemia	- Suspect it when abdominal symptoms occur in patients with cardiovascular and atherosclerotic risk factors
SIBO	- Increased prevalence in older people, mainly if with history of abdominal surgery or other causes responsible for an impaired intestinal motility - Suspect it in case of nonspecific abdominal distention, bloating, and chronic diarrhea

Figure 4. Main take-home messages relative to more common small bowel conditions in older people. Abbreviations: SIBO = Small Intestinal Bacterial Overgrowth.

4.3. Lower Gastrointestinal Tract Diseases

4.3.1. Diverticular Disease

Diverticular disease is a common and heterogeneous clinical condition arising from the presence of symptomatic diverticula of the colon, mostly representing an age-dependent illness. Indeed, while it is uncommon under the age of 40, its prevalence increases progressively with age, reaching 70% in people aged over 85 [80,81]. This is related to the age-related changes in the connective tissue of the colonic wall and a complex interplay between colon microbiota, inflammation, visceral hypersensitivity, and colonic motility.

The diverticular disease manifests itself with a wide spectrum of clinical manifestations, ranging from symptomatic uncomplicated diverticular disease (SUDD) to acute uncomplicated and complicated diverticulitis (with perforation, abscess, strictures, or fistulas), diverticular bleeding, and segmental colitis associated with diverticulosis (SCAD) [80]. Although diverticular disease has generally been considered an acute or episodic disorder requiring a surgical approach, a growing body of evidence is shifting the paradigm from an acute illness to a chronic bowel disorder characterized by vague abdominal symptoms and recurrent flares with considerable psychosocial impact [82]. In particular, SUDD can present with abdominal symptoms attributed to diverticula in the absence of macroscopically overt colitis or diverticulitis, such as lower discomfort or abdominal pain, bloating, abdominal tenderness, constipation, diarrhea without any sign of inflammation (fever, neutrophilia, and diverticular inflammation [80]) that can mimic other gastrointestinal disorders, such as irritable bowel syndrome (IBS). Moreover, recent evidence showed that diverticulitis is less likely to become complicated in the elderly when compared with younger populations [83]. These developments are prompting a shift also in therapeutic approaches from widespread antimicrobials, supportive care, and surgical approaches in acute phases, as stated by current guidelines, to the use of probiotics, mesalamine, and gut-directed antibiotics in chronic forms. Indeed, many studies are supporting the use of mesalamine, given its inflammatory properties, and rifaximin, a broad-spectrum poorly absorbed antibiotic, in symptom relief and prevention of recurrence in uncomplicated diverticular disease [83]. Finally, it is important to highlight that, in the latest guidelines on diverticular disease, the role of probiotics has been reconsidered [84,85]. The key role of strict adherence to the diet has also been partly reduced. Eberhardt et al. reported with a low level of evidence that a high dietary fiber intake (>29 g/day) may improve gastrointestinal function in patients with SUDD [84]. However, the GRADE (grading quality of evidence and strength of recommendations) level of evidence was low [85].

4.3.2. Inflammatory Bowel Diseases

Inflammatory bowel diseases (IBDs) encompass chronic inflammatory conditions affecting the gastrointestinal tract, including Crohn's disease and ulcerative colitis (UC). Their prevalence is increasing worldwide, particularly in older age. Up to 15% of newly diagnosed patients in the US are over 65 years [86,87], but the incidence may be underestimated due to a subtler disease presentation in this age group and a wide range of differential diagnoses. In the older IBD population, ulcerative colitis (UC) has a higher incidence (12.5%) than Crohn's disease (CD) (5%). Apart from individuals suffering from IBD—diagnosed at a young age—with disease progression, there is an increase in the incidence of patients with new onset disease just after the age of 65. Elderly-onset IBD differs in clinical manifestations and courses from younger-onset IBD, with predominance of colonic disease, milder course, and less frequent occurrence of extraintestinal manifestations. However, IBD occurring in the elderly poses specific challenges to clinicians related to the presence of comorbidities, lower functional reserves, and a higher risk of treatment-related complications.

Elderly-onset CD presents a more frequent colonic localization rather than ileocolic and predominantly inflammatory pattern [88,89]. As a consequence, rectal bleeding is more frequent, while symptoms of abdominal pain, diarrhea, weight loss, and fever are less likely to be present. UC presents more frequently with left colitis rather than pancolitis, and the disease tends to remain stable, with only a small fraction of patients showing disease extension at follow-up [89]; it also presents less frequently with rectal bleeding and abdominal pain than younger patients.

Diagnostic work-up in the elderly does not differ from younger subjects, but the evaluation of these patients aims to exclude other causes such as malignancies (cancer and lymphoma), infectious disease, ischemic colitis, microscopic colitis, segmental colitis associated with diverticular disease or side effects of nonsteroidal anti-inflammatory agents. There are no indications in the guidelines regarding this specific population. Since the elderly IBD population is often excluded from clinical trials, safety and efficacy data about medications for IBD remains limited. Moreover, studies often do not distinguish between elderly patients already suffering from IBD with disease progression and elderly onset IBD, which may have different disease courses [90]. Even if endoscopic remission is the target of treatment as established by current guidelines [91], in the older population, it is currently acceptable to tolerate mild endoscopic disease activity, in consideration of the shorter life expectancy and lower possibility of developing long-term complications [92].

Regarding the therapy of IBD in the elderly, it must be kept in mind that some medications can cause a greater number of side effects in this specific population due to the physiological changes related to aging, the patient's frailty, the presence of comorbidities, and the concomitant intake of other drugs.

Corticosteroids represent a pivotal point of IBD therapy, useful especially in acute phases and in inducing remission. However, their long-term use is associated with multiple side effects, more often in the elderly than in young adults [93], including the onset of metasteroidal diabetes (or a worsening in the glycemic control in diabetic patients), worsening of the blood pressure profile in patients suffering from hypertension, increased risk of opportunistic infections, osteoporosis, the onset of cataracts, glaucoma, and avascular necrosis. Despite this, older patients with IBD are often under chronic steroid therapy [93], probably for a higher level of confidence of the clinicians towards these drugs. Budesonide, characterized by a first-pass hepatic effect, presents fewer side effects than other steroids and should be considered as a viable option in mild-moderate disease.

The use of aminosalicylates is considered a safe option for older patients with IBD; indeed, about 40 to 75% of older IBD patients take aminosalicylates [90]. Current guidelines support their use in UC, but their use in CD remains controversial. However, given their good safety profile, prescriptions in older people with mild-moderate CD are increasing. Side effects include a low risk of nephrotoxicity, which may be significant in older patients with pre-existing kidney disease or other potentially nephrotoxic drugs [94]. In addition, older patients could experience discomfort in taking multiple pills per day or difficulty in self-administration of rectal formulations. Regarding thiopurines, methotrexate, and cyclosporine, their use in the elderly is burdened by an increased risk of side effects [93]. In the case of moderate to severe IBD, treatment with anti-TNF therapy (i.e., infliximab and adalimumab) is indicated to induce and maintain remission in young and adult patients. However, various studies assessing the safety and efficacy of these drugs in the elderly showed an increased risk of adverse events [95]. Among these studies, Cottone et al. have shown that anti-TNF agents increase the risk of infection, neoplasms, and mortality in the elderly [96]. Anti-TNF agents are also contraindicated in patients with NYHA III-IV heart failure and may cause exacerbation of heart failure, a condition more common in the elderly than in young people. Another agent approved for moderate–severe forms of UC and CD is vedolizumab, a monoclonal antibody that binds to integrin $\alpha 4\beta 7$ that reduces intestinal inflammatory activity [97]. Post hoc analysis of dedicated trials, GEMINI 1 and 2, showed similar efficacy of this drug among younger patients and patients aged > 55 years;

however, the number of patients aged > 60 years was low. There were also no significant increases in infections, neoplasms, or infusion-related reactions between age groups [98].

Although some studies show that the elderly onset IBD has a less aggressive course [99], older people with UC undergo more frequent surgical treatments than younger people [100]. The indications for surgery in the elderly are the same as in younger patients: a refractory disease or a fulminating course, the presence of neoplasms, or major intestinal bleeding, but morbidity and perioperative mortality are higher than in the younger counterparts.

Growing evidence supports the potential role of dysbiosis of the gut microbiota in the pathogenesis of IBD. For this reason, fecal microbiota transplantation (FMT) has been investigated as a promising treatment strategy lately [101]. Results from some randomized controlled trials (RCTs) showed beneficial effects on patients with UC. While in CD, RCTs are missing [101], the literature still brings hope and highlights the potential of FMT even in CD [102]. Furthermore, FMT shows promise in other pathologies such as Parkinson's disease and colorectal cancer, common conditions in the elderly that are linked to microbiome changes [103]. In any case, in most of the studies currently available on FMT, older IBD patients are generally under-represented or absent [104].

4.3.3. Microscopic Colitis

Microscopic colitis (MC) is a common cause of chronic diarrhea in older people. It is caused by inflammation of the colon and encompasses two different subtypes, namely, lymphocytic colitis (LC) and collagenous colitis (CC) [105,106]. The incidence of MC increases with rising age. A recent meta-analysis showed that the median patient's age at the time of diagnosis was 65 years [107]. It should be suspected in middle-aged to older patients, especially females and with a personal or familial history of autoimmune diseases, presenting nonbloody, watery diarrhea, with nocturnal stools, fecal urgency, fecal incontinence abdominal pain, arthralgias, and weight loss [105,108]. Its pathogenesis is unclear, but smoking and several drugs, as well as NSAIDs, PPIs, and statins, have been considered trigger factors in genetically predisposed individuals [105,106]. The diagnosis relies on the exclusion of other causes and histologic evaluation. First-line treatment in moderate to severe disease is represented by budesonide, which can induce remission; however, long-term maintenance treatment is often required due to the high rate of relapse upon discontinuation [105,106]. Immunotherapy can be considered for refractory diseases [105,106].

4.3.4. Irritable Bowel Syndrome

Irritable bowel syndrome (IBS) is one of the most commonly encountered functional gastrointestinal disorders, characterized by abdominal pain and altered bowel habits in the absence of any organic abnormalities, either structural or biochemical. Epidemiological studies highlight that the prevalence of IBS is similar across different age groups, but the incidence is highest during adolescence and young adulthood, while new onset disease after the age of 65 is rare. A prospective study conducted on 230 patients who were referred to geriatric clinics demonstrated that although approximately a quarter of the patients presented with symptoms compatible with IBS and had negative investigations, the diagnosis was practically never made, resulting in undertreatment of the problem in this age group [109]. The clinical presentation and diagnosis in the elderly do not differ significantly from the young subjects, although bowel changes in the elderly tend to be intermittent, with a greater prevalence of constipation, and the perception of pain in this group is often altered [110]. The diagnosis of IBS usually relies on symptom-based diagnostic criteria known as the Rome criteria. However, in the elderly, it is advisable to adopt a careful and cautious diagnostic approach given the higher prevalence of organic pathologies, comorbidities, and polypharmacy, which can affect the gastrointestinal tract [110]. Furthermore, extraintestinal pathologies, such as chronic prostatitis in men, can also mimic symptoms of IBS. All these aspects must be taken into consideration, and an extensive evaluation of possible alarm symptoms must be carried out, taking into account that these can be

present regardless of the presence of IBS. Moreover, aging itself is considered one of the alarm symptoms. As a result, IBS is primarily a diagnosis of exclusion in this age group. The treatment does not differ significantly from young patients and is based on the use of selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants, but with greater caution because of side effects and drug interactions [110], with special regard to tricyclic antidepressants, which can cause urinary retention, closed-angle glaucoma, and cognitive impairment due to their anticholinergic properties [111]. Since multiple lines of evidence support the hypothesis that alterations in the gut microbiome could play a role in the genesis of IBS symptoms, the effectiveness of FMT as a potential treatment has been studied in some works [112]. The results are interesting but limited by low quality and small sample size; for this reason, the FMT for the treatment of IBS is not currently recommended by the guidelines [113]. Large, multicenter, double-blind, placebo-controlled studies are required, as well as a greater inclusion of elderly patients, poorly represented in the currently available studies.

4.3.5. Gut Infections

As previously highlighted, the elderly are at greater risk of being affected by gut infections due to an impairment of mucosal defense mechanisms. Clostridioides difficile infection (CDI) disproportionally involves older people with a higher risk for recurrent CDI (rCDI). As early as 2009, a statistical brief documented the incidence of CDI-related hospital stays for adults aged 65 to 84 years and 85 years or older was 4- and 10-fold greater, respectively, than for adults aged 45 to 64 years [114]. The higher incidence in the elderly is due to the following risk factors: age-related impairment of the immune system, increasing antibiotic utilization, frequent health care exposure, immunosenescence, and different composition of the microbiota compared to the adult younger, with fewer competing anaerobes such as Bacteroides and Bifidobacterium [114].

The goals of successful treatment are the elimination of symptoms and the prevention of recurrent CDI. Treatment of CDI is based on antibiotic therapy with oral vancomycin, metronidazole, or fidaxomicin; the choice depends on disease severity, history, number of recurrences, and drug cost. Bezlotoxumab, a recently approved monoclonal antibody targeting C. difficile toxin B, can be useful for patients who are at high risk for rCDI.

Relapse of CDI occurs in 10–25% of patients treated with metronidazole or vancomycin, with multiple relapses in 40% of patients [115].

In recent years, fecal microbiota transplantation (FMT) has emerged as a highly effective treatment of severe, fulminant, recurrent, or refractory forms of CDI, with high efficacy and an overall high safety level. The cumulative experience from case series and controlled trials shows that FMT is effective (80–90%) and safe when used to treat relapsing CDI, also in frail and very old patients [116,117].

Whipple disease, caused by Tropheryma whipplei, is another infection with a higher frequency in elderly people than in the adult population: prevalence was 7.9 cases per 1 million in individuals $\leq$65 years old compared to 24.4 cases per 1 million in individuals >65 years old [118]. In fact, older individuals are more inclined to have the immune structure necessary for Whipple's disease manifestation. The increase in antibiotic use may mask clinical Whipple's disease for a period of time with later manifestation [118]. The disease causes abdominal pain, weight loss, steatorrhea, joint symptoms, and systemic features. The diagnosis is based on a biopsy of the lymph node or small bowel. Successful treatment can be achieved in most cases by antimicrobial therapy (doxycycline and hydroxychloroquine, ceftriaxone, and meropenem).

4.3.6. Colon–Rectal Cancer

Colorectal cancer (CRC) is the third most commonly diagnosed cancer in males and the second in females [119]. Age is a major risk factor for sporadic CRC: forty-two percent of new diagnoses of CRC are in patients aged 65 years and older, and the incidence is higher in men than women. Apart from age and male sex, other risk factors have been identified: family history of colorectal cancer, inflammatory bowel disease, smoking, excessive alcohol consumption, high consumption of red and processed meat, obesity, and diabetes [120]. The typical symptoms of colon cancer are a change in bowel habits (i.e., diarrhea or alternating diarrhea/constipation), evidence of blood loss from the intestinal tract (hematochezia and rectorrhage), abdominal pain, and unexplained iron deficiency anemia. Regarding screening for CRC, current guidelines suggest stopping colonoscopy screening at the age of 75 years and no screening above 85 years [121]. For a correct approach to CRC therapy in the elderly, it is essential to consider their clinical conditions, overall frailty, and functional status, which are not adequately represented only by age. In order to make an assessment of the general and functional status as complete as possible, geriatricians use the comprehensive geriatric assessment (CGA) scale to identify fragile patients at greater risk of adverse outcomes [122]. An older fit patient can be treated with the same treatments as a younger adult patient, with tighter follow-up and a few more precautions. For example, minimally invasive surgery, such as laparoscopic colectomy, would be preferable, and chemotherapy requires careful monitoring for adverse events. Like the younger adults, therapy for the elderly is based on surgery, neoadjuvant radiotherapy (in the case of rectal cancer), and adjuvant chemotherapy (for patients with stage III/IV and high-risk stage II colon cancer). Advanced and metastatic colon cancer requires the evaluation of the functional status as well as the estimated life expectancy in order to decide the best strategy to adopt. In this case, palliative chemotherapy improves progression-free survival (PFS) and overall survival (OS).

4.3.7. Constipation

Chronic constipation is a common disorder characterized by difficult or incomplete evacuation, hard stool, or reduction in stool frequency. It negatively impacts on quality of life, with psychological and social consequences. Risk factors include age, female gender, physical inactivity, medication use, depression, institutionalization, and low education and income [123,124].

A population-based study reported that the cumulative incidence is lower in the younger (~20%) compared to the older population [125] until a prevalence ranges from 50 to 70% in residents of elderly care institutions. This difference is due to age-related alterations (reduced plasticity, compliance, macroscopic structural changes such as diverticulosis, altered control of the pelvic floor, slow colonic transit, electrolyte, and metabolic imbalance), endocrine dysfunction (i.e., hypothyroidism) and neurodegenerative diseases involved in colonic neuropathy and myopathy (i.e., Parkinson disease). Functional constipation is currently defined by Rome IV criteria, according to objective and subjective criteria over a specific time period [126]. Distinction with "IBS with constipation" may be difficult, but generally, patients with "IBS with constipation" have a more prominent abdominal pain symptomatology [127]. Pelvic floor dysfunction and slow colonic transit are the two major etiologies of functional constipation [128,129]. In an epidemiological study by Arco et al., 384 patients aged over 70 years recruited from the community, a hospital, and a nursing home were stratified according to Fried's frailty criteria and evaluated the presence of functional constipation, stool consistency, comorbidities, dependency, and quality of life. Functional constipation prevalence in older adults was high (26.8%), particularly in women (57.3%), and was significantly associated with frailty and quality of life [129]. Moreover, regarding clinical manifestations, nonfrail and prefrail patients presented prevalently slow colon transit time features, while frail patients reported more functional defecation disorders frequently [129].

Also, polypharmacy is a major risk factor for constipation in the elderly [1]. Multiple drugs can interfere with colonic motility. Opioid analgesics, calcium channel blockers, tricyclic antidepressants, diuretics, vinca alkaloids, and other drugs may alter both small intestine and colonic motility. For these reasons, before starting any specific therapy in an older patient, it is important to consider other factors that impact constipation, such as polypharmacy, dehydration, dementia, etc. Treatments for chronic constipation include stool softeners, fiber supplements, osmotic and stimulant laxatives, and the secretagogues lubiprostone and linaclotide. Generally, fiber supplementation is a reasonable initial therapeutic approach; however, in unresponsive patients, it can be advanced to osmotic laxatives. Eventually, stimulant laxatives and prokinetic agents should be reserved for patients who are refractory to fiber supplements or osmotic laxatives [128]. Chronic and untreated constipation can lead to fecal impaction, a condition potentially responsible for serious complications, such as bowel obstruction, perforation, peritonitis, and shock [130]. Fecal impaction primarily affects older people, incapacitated patients, and children. Unspecific symptoms, such as abdominal distension and pain, nausea, vomiting, and paradoxical diarrhea, and the inability of patients to communicate their discomforts effectively may contribute to a delayed diagnosis. A careful medical history and an accurate, objective examination, in addition to an abdominal radiographic examination or a CT scan can correctly orient the diagnosis [130]. Treatments include manual maneuvers to fragment and extract the fecal mass, distal colonic cleansing with enemas, and rectal lavage with a sigmoidoscope. In case of peritonitis resulting from bowel perforation, surgical resection of the involved intestine tract is indicated [130]. Since fecal impaction is a recurrent condition, it is important to prevent other events with dietary measures (increase in fiber intake), pharmacological interventions (laxatives), or correct underlying anatomical factors [130].

4.3.8. Fecal Incontinence

Fecal incontinence is the unintentional passage of stools, solid or liquid. The prevalence of this condition increases with age and is higher in hospitalized and institutionalized elderly patients, reaching 18–33% in hospitals and 50–70% in nursing homes [127]. Risk factors associated with fecal incontinence include old age, dementia, cognitive disorders, reduced mobility [127], stroke [131], urinary incontinence [132], and multidrug therapy [133].

Fecal continence is obtained by the coordinated action of sphincters (internal and external), muscles (puborectalis muscle of the levator ani complex), rectal compliance, and sensory stimuli from the recto-anal tract. An alteration of one or more of these components, such as an anal sphincter iatrogenic or obstetric lesion, reduced rectal compliance and/or rectal sensation, and the presence of diarrhea, can cause fecal incontinence [133].

Fecal incontinence has a considerable negative impact on the quality of life and can be responsible for psychological distress with social consequences [127]. In fact, patients often limit their life activities due to this condition, and a considerable number of patients do not talk about that with a physician or relatives; so, it is important to ask an older patient directly whether she/he is affected by fecal incontinence [127]. Management includes getting an accurate history, laboratory tests, stool tests, and, if there is a suspicion of a discariokinetic underlying process, endoscopy and biopsy [127]. Also, anorectal manometry can be performed to evaluate the function of the rectal and anal muscles [127]. Education and lifestyle modification such as dietary intervention (trigger food avoidance and increase in fiber consumption), using pads for protection, squeezing exercises, hygiene advice, and discontinuation of potentially laxative drugs are the first steps of treatment, followed by medication to increase stool consistency (psyllium and loperamide) [127]. Among other therapeutic options, sacral nerve stimulation is the most widely used treatment and consists of an implantation of a stimulating electrode through the sacral foramina, modulating colonic and urinary function locally and via central nervous activity [134].

The main take-home messages relative to the abovementioned lower gastrointestinal tract conditions in older people are summarized in Figure 5.

More common lower gastrointestinal tract conditions in older people - Main take-home messages -	
Diverticular disease	- A very common condition in older people, usually associated with a lower risk of complication with respect to younger people
IBD	- Same diagnostic work-up as in younger subjects - Carefully evaluate a long-term steroidal therapy since side-effects - No definitive results about safety with anti-TNF agents in comorbid older adults
Microscopic colitis	- To be suspected in middle-aged to older patients, mainly female and with a personal or familiar history of autoimmune diseases with non-bloody and watery diarrhea
IBS	- New onset disease after the age of 65 is rare. A careful differential diagnosis should be performed before confirming the diagnosis
Infections	- Elderly patients are at great risk, mainly for *C.difficile* infection - FMT is also considered safe in old and very old populations
Colon-rectal cancer	- Age is a major risk factor for sporadic CRC - Screening colonoscopy should be stopped at the age of 75 years - Evaluate overall patient's functional status and comorbidity, besides age, to choose the best strategy
Constipation	- More frequent in the elderly. Consider predisposing factors, such as polypharmacy, dementia, dehydration, hypomobility, and bad dietary habits
Fecal Incontinence	- Prevalence increases with age, mainly in hospitalized and institutionalized older patients - Consider predisposing factors, such as dementia, cognitive disorders, reduced mobility, stroke, urinary incontinence, and multidrug therapy

Figure 5. Main take-home messages relative to more common lower gastrointestinal tract conditions in older people. Abbreviations: CRC = Colon-Rectal Cancer; FMT = Fecal Microbiota Transplantation; IBS = Irritable Bowel Syndrome; IBD = Inflammatory Bowel Diseases; TNF = Tumor Necrosis Factor.

5. Discussion

Age-related changes involving the GI system are associated both with structural and functional alterations, thus leading to modifications in the body's ability to digest, absorb, and excrete nutrients.

A rigorous and detailed diagnostic work-up should always be encouraged in older subjects complaining of GI symptoms to rule out specific diagnoses rather than be attributed only to a normal aging process. As an example, the higher incidence of dysphagia in the elderly is commonly related to changes in structure and physiology usually occurring with advancing age. Nevertheless, rather than be automatically considered a normal finding in healthy aging, dysphagia itself represents an alarm symptom, mainly if associated with other signs like sudden weight loss, dysgeusia, or anemia and a history of smoking and alcohol abuse. In the same way, in the case of dyspepsia, upper gastrointestinal endoscopy is strongly recommended in patients aged over 60 years unless they are too frail since organic diagnoses are more likely compared to functional ones in this age group.

In any case, knowledge of the pathophysiological mechanisms underlying GI diseases must be necessarily complemented by a careful evaluation of the patient's medical history and functional status. In fact, while some GI conditions share the same mechanisms between young and older people, they deserve peculiar management in most older and frail subjects. In the case of celiac disease, as an example, diagnostic work-up and specific treatment are similar between younger and older patients, but the risk of complications of the disease is significantly higher in the latter group, mainly because of the deleterious consequences of nutrient malabsorption. Neurological and bone metabolism complications result in an increased risk of falls and fractures, as well as iron-deficiency anemia may result in worsening of functional status, mainly in the presence of concomitant cardiovascular

diseases. Therefore, clinicians should be well aware that the global treatment of an older celiac patient may be more complex than the disease treatment per se. Also, for IBDs, the diagnostic process is similar among the age categories; however, considerations about the side effects of specific therapy are mandatory, above all as regards steroids. The onset of metasteroidal diabetes, or a worsening in the glycemic control in diabetic patients and of the blood pressure profile, the increased risk of opportunistic infections, osteoporosis, the onset of cataracts, glaucoma, and avascular necrosis, may be carefully evaluated prior to choosing the best strategy to adopt.

Different GI conditions may manifest themselves with nonspecific, nuanced symptoms, mainly in the elderly, making the diagnostic process in this category more complicated. In the case of GERD and peptic disease, for example, the clinical presentation is often atypical, resulting in diagnostic delay and increased development of complications. Moreover, older subjects with SIBO and IBS may complain of nonspecific abdominal distention, bloating, and poorly localized discomfort. Whether ruling out organic diseases is mandatory in this age group, it does not consequentially lead to achieving a final diagnosis, thus resulting in an undertreatment of the problem. Instead, a detailed medical history may help clinicians recognize typical factors of advanced age related to a higher risk for conditions such as SIBO, which are reduced gastric secretion (due to a larger use of PPIs), impaired GI motility, intestinal surgery, and small bowel diverticulosis [56]. A complete approach to these conditions, both in the phase of diagnosis and therapy, may undoubtedly improve health status and quality of life, both of them representing fundamental outcomes in older subjects.

So, the difficulty in managing older patients with gastrointestinal diseases derives from many factors. The clinical presentation and the multiple comorbidities can complicate the clinical picture; therefore, it is important to weigh and personalize diagnostic and therapeutic choices.

In this context, the role of endoscopy in older adults has expanded in recent years because of the increased burden of age-related gastrointestinal and biliary disorders, with particular regard to gastrointestinal malignant diseases. Gastric and colon–rectal cancers are considered age-related diseases, with a peak of incidence between the ages of 60 and 80 years, and are leading causes of morbidity and mortality worldwide. When it comes to the safety of endoscopy in the elderly, caution should be taken when administering sedation, but advanced age cannot be considered a contraindication per se. A study by Clarke et al. involving patients aged 85 years or more showed that elective and emergency endoscopic procedures (colonoscopy, esophagogastroduodenoscopy, and cholangiopancreatography) are safe without increased postprocedure-related adverse events [135]. Another study by Finkelmeier et al., involving 758 patients aged 80 years or older who underwent ERCP procedures for gallstones or tumor obstruction of bile ducts, has demonstrated that ERCP is safe and efficient, and the incidence of post-ERCP pancreatitis is lower in older patients compared with younger ones [136]. Overall, endoscopic investigations are ethically justified in the elderly when it is expected that the results will influence either clinical management or disease outcome, and the benefit from the procedure outweighs the risks involved.

Another relevant concern in older patients is the "polypharmacy" topic, which predisposes them to a more complicated clinical course and increases the probability of the development of complications. Older patients, in consideration of comorbidities, are more frequently prescribed a large variety of drugs, such as NSAIDs and aspirin, that are associated with dyspepsia and peptic disease. Therefore, while the incidence of conditions, such as peptic disease, is decreasing in the general population, the rate of complications, hospitalization, and mortality for gastric and duodenal ulcers remains high in older patients. Another relevant problem associated with polypharmacy is pill esophagitis, which is mostly described in older adults and typically presents with odynophagia, chest pain [137], and ulceration at endoscopy. It is frequently associated with NSAIDs, aspirin, bisphosphonates, ferrous sulfate, and captopril. Risk factors most commonly associated with pill esophagitis are motility disorders, compression of the esophagus (i.e., cardiomegaly), and taking medication with insufficient amounts of water [138].

Multiple drugs can also interfere with colonic motility: Opioid analgesics, calcium channel blockers, tricyclic antidepressants, diuretics, vinca alkaloids, and other drugs may alter both small intestine and slow down colonic motility. In reverse, laxatives, metformin, NSAIDs, simvastatin, levodopa benserazide, colchicine, and digoxin [139] can cause diarrhea. An interesting form is the sprue-like enteropathy associated with the assumption of olmesartan, which usually presents with fatty diarrhea and can lead to malabsorption [140].

In consideration of all these aspects, the drugs administered to older patients need to be weighed on their complexity. For example, PPIs are among the most commonly used medications for the treatment and prevention of acid-mediated upper gastrointestinal conditions. These drugs are overall well tolerated and safe [141]; however, lifelong PPI therapy should be carefully considered according to current guidelines [141], balancing clinical benefits and possible side effects in the elderly, such as enteric infections [142], including hospital- and nursing home-acquired C. difficile [143–145].

Regarding gastric and colon–rectal cancer, usually considered age-related diseases, the correct approach is far from being standardized. Age itself cannot be sufficient to direct the best strategy to adopt, while a combination of evaluation of patients' overall frailty, functional status, and estimated life expectancy should always be performed.

Finally, clinicians must know and recognize some GI conditions that are more likely to occur in older subjects and associated with typical risk factors of advancing age, such as chronic mesenteric ischemia and C. difficile colitis. Growing awareness about risk factors such as hypertension, diabetes mellitus, and dyslipidemia in the case of the first condition, as well as inappropriate use of antibiotics in the second condition, may actually represent the target for disease prevention rather than only treatment.

6. Limitations of the Study

This review has some limitations. Firstly, since the magnitude of the topic, we necessarily had to delve into the most frequent disorders rather than being able to deal with every single disease. For example, we chose not to include liver, biliary, and pancreatic diseases only for length reasons, although we are aware of the importance for clinicians to know about their peculiarities in the elderly. Therefore, we think that these arguments may deserve a detailed and separate work. Secondly, we tried our best to summarize and give a series of practical take-home messages relative to the eventual peculiar features of the most frequent gastrointestinal conditions in the elderly. However, it does not imply that, above all, for the frailest and comorbid subjects, a personalized approach should be encouraged, and the overall management may not be generalized a priori.

7. Conclusions

In the context of GI diseases, the management of older patients may represent a challenge for all physicians. Although some GI conditions may share the same clinical picture between younger and older adults, a personalized diagnostic and therapeutic approach should be required based on the overall older patient's functional status and other comorbidities. Moreover, multiple comorbidities and side effects of polypharmacy can often interfere with the differential diagnosis, making it more difficult to distinguish normal aging processes from pathological diagnosis.

For this reason, a comprehensive multidimensional assessment should always be encouraged in older people with a suspected or confirmed gastrointestinal disease in order to support physicians both in the diagnostic process and in global management.

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