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Ulcerative Colitis in the Elderly. A Practice Update

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Abstract

Incidence and prevalence of inflammatory bowel disease is rising around the world, both in
general population and in elderly patients. In this age group, ulcerative colitis is more frequent than Crohn's disease.
Many diseases typical of geriatric age mimic ulcerative colitis, and differential diagnosis may be challenging.
Elderly-onset ulcerative colitis has a milder clinical presentation. Abdominal pain, rectal bleeding and fever are less common. At the time of diagnosis, left-sided ulcerative colitis is the more frequent disease location.
Therapeutic strategies may be complex, and their choice influenced by comorbidities and polypharmacy.
Aminosalicylates and steroid use is similar in old and adult patients. Immunomodulators and biological agents are less used, while elderly patients are more likely to be hospitalized and to undergo surgery, with a higher rate of hospitalization and surgery related complications.
Malignancies, infections and mortality are also more frequent in the elderly.

Key Words: ulcerative colitis; elderly; comorbidity; polypharmacy; therapeutic strategies; surgery

Introduction

Prevalence and incidence of inflammatory bowel disease are increasing world-wide [1].
Also the number of elderly patients affected by UC and CD is increasing, because global population is aging and IBD represent a chronic condition [2]. Moreover, compared to past years, IBD are now taken into account as a diagnostic hypothesis in this particular age group.

Despite the fact that most IBD are diagnosed during young and adult age, up to 25-35% of IBD patients are ≥ 60 years old, of whom 15% received IBD diagnosis during old age [3,4].
UC incidence is about 1,1-16,5/100000, while CD incidence is about 0-18,9/100000 [2].

The prevalence and incidence of IBD is rising all over the world, but these data are different in developed and developing countries. (Table 1)
Different data shown in some studies could be due to the lack of unclear definition of "elderly". Some studies report 65 years old as a threshold value [10 11], while most accepted age is now considered 60 years old [12].

In elderly-onset IBD, UC is more frequent than CD (11-21% vs 5-17%) [12,13].
Our review focuses on ulcerative colitis and on main differences between elderly-onset and adult-onset ulcerative colitis.
Differences in many aspects are reported in literature: disease extension, natural history and disease course, comorbidity and polypharmacy, hospitalization, therapeutic strategies, adverse drug reactions, need for surgery, infections, mortality.

Nation	CD	UC
France [5]	2,6/100000	3,1/10000
Hungary [6]	3,04/100000	10,8/100000
Sweden [7]	10/100000	19/100000
Canada [8]	18,9/100000	16,5/100000
Asia-Pacific [9]	0,3/100000	0,8/100000
Holland [3]		23,66/100000

Table 1: CD and UC incidence

Differential Diagnosis

Ulcerative colitis is more frequent in male patients (56,8%) [3,14,15]. but as well as general population, even in elderly patients, more frequent diagnostic delay is reported (up to 6 years) [12,16]. The more frequent delay could be due to several reasons: many conditions typical of geriatric age can mimic UC symptoms [13]; elderly-onset UC with milder clinical presentation, tend to be underestimated, in particular if there are other concomitant diseases; access to specialist healthcare may be more difficult for some patients, especially who lives in a disadvantaged family, social and economic context [12].
Ulcerative colitis needs to be differentiated by infectious colitis, colitis related to NSAID-use, ischaemic colitis, segmental colitis associated with diverticulosis, radiation colitis, lymphocytic and collagenous colitis, diversion colitis, solitary rectal ulcer syndrome. (Table 2)

Correct diagnosed can be reached considering symptoms, risk factors, concomitant disease and concomitant drug use [17,18].

Disease	Symptoms	Risk factors/differences	Endoscopic findings
Infectious gastroenteritis	Diarrhea with/without blood Fever	Positive stool cultures History of antibiotic use Travels	Variable findings (e.g. Pseudo-membranes in C. Difficile infections)
NSAID-induced colitis	Diarrhea with/without blood Abdominal pain Obstruction	NSAID use	Isolated lesions affecting any part of intestine
Ischemic colitis	Bloody diarrhea and abdominal pain associated with food intake	History of cardiovascular/metabolic disease	Clear separation between normal and affected mucosa Splenic flexure and left colon often involved Rectal sparing
Diverticular disease	Bloody diarrhea Abdominal pain	History of diverticular disease	Inflammation around diverticula
Radiation colitis	Bloody diarrhea Abdominal pain Tenesmus	History of radiotherapy	Multiple telangiectasia more frequently located in rectum and sigmoid colon
Lymphocytic and collagenous colitis	Diarrhea without blood	PPI, statin use	Normal
Diversion colitis	Abdominal pain and discharge with blood and mucous may be present	Previous bowel surgery determines inflammation of defunctionalized bypassed colon	Variable findings (erythema, diffuse granularity, blurring of vascular pattern, mucosal friability, aphtous ulceration, bleeding
Solitary rectal ulcer syndrome	Rectal bleeding Straining	History of constipation	Rectal ulcer

Table 2: UC differential diagnosis

Clinical Presentation and Natural History

UC clinical presentation is different between elderly and adults. Abdominal pain, rectal bleeding and fever are less common in the elderly, while anaemia and weight loss are more common [3,10,14,19,20].
Thus, first presentation can be more severe with a higher rate of hospitalization at diagnosis [3,14].
Prevalence of extraintestinal manifestations is lower [21,22,23]. (9.6% vs 19.2% [24]).
Left sided UC is more common (45%), rather than pancolitis (31%) and proctitis (22%). Other studies confirmed left sided UC as the most frequent presentation (45-61,3%), followed by pancolitis (17,9-26%) and proctitis (20,7-29%). Disease extension tend to remain stable during disease course (84% patients had no disease extension during follow up) [3,14,15,22,23,25].

Some studies analyzing UC natural history show that UC tend to

be less aggressive in the elderly, as immunomodulators and biological therapy are less used [24]. Despite this, higher surgery rates may suggest that these therapies are less used because of comorbidities and physician hesitancy rather that a less aggressive disease course [20].

Multimorbidity and Polypharmacy

Multimorbidity is frequently reported in elderly patients (presence of 2 or more chronic diseases). Most frequent diseases are represented by congestive heart failure, hypertension, diabetes, chronic obstructive pulmonary disease, cancer, psychiatric/neurological disease, renal impairment, infective diseases [17,26].

As a consequence of these condition, also the number of drugs taken is higher in the elderly [27]. In a cohort study, 40% of elderly patients had drug interaction involving UC specific therapy [28].

Polypharmacy increases drug interaction (increased risk of adverse reactions; altered drug metabolism) and reduces adherence to therapy, with a higher rate of complications [29]. In addition, depression or neurological disease such comorbid condition common with age, can alter adherence to therapy.
Therapy choice can be driven by some pre-existing conditions, such as hypertension, heart failure, diabetes, psychiatric disorder, renal failure, malignancy, as they may be worsened by some specific UC drugs [5].
Drug metabolism may be altered by some physiological changes typical of geriatric age: altered fat/lean mass ratio, reduced glomerular filtration rate, hypoproteinemia, with reduced drug-binding capacity [30].
Finally, some specific UC drugs are poorly accepted even by the elderly patients (for example, topical therapy). For this reason, specific formulation should be avoided or adjusted (e.g. reduce volumes of enema) [31].

Hospitalization

Elderly patients are more likely to be hospitalized.
They have longer hospital stay and they report more frequently hospitalization-related adverse events (anaemia, malnutrition, hypovolemia) and disease-related adverse events (surgery-related complications, deep vein thrombosis), with more difficult post-hospitalization recovery [32,33,34].
In a study conducted by Komoto et al., UC-related hospitalization were more frequent in the elderly (54.2% vs 35.7%; $p < 0.001$) [35].

Therapeutic Strategies

Therapeutic approach differs between elderly and adults.
First of all, elderly patient should be divided into fit elderly and frail elderly. UC management and therapeutic options could be very different in these two subgroups, as comorbid conditions and number of drugs taken can influence many therapeutic options commonly used in UC [16,18].
Elderly-onset UC seems to have a milder clinical course [6,36]. This is witnessed by a lower use of immunomodulators and biologic therapies. Despite this, higher surgical rates may suggest that UC hasn't a milder course [20,25]. but it may express a greater reticence in immunosuppressant/biological therapy use, as they may be contraindicate for comorbidities or higher risk of adverse events.
Different drugs used in elderly-onset ulcerative colitis, indication, limitation and interactions are summarized in table 3.

Therapy	Indications	Limitations	Drug interactions	Additional information
Aminosalicylates	Induction/maintenance of remission in mild-moderate UC	Renal failure	Warfarin Digoxin Hydralazine Anti-tuberculosis drugs [41], 6-thioguanine	Prefer once-daily subministration Prefer oral therapy
Corticosteroids	Induction of remission in moderate-severe UC/previous failure to aminosalicylates	History of diabetes, hypertension, neurological/psychiatric disease, infections	Phenytoin, phenobarbital, rifampicin, warfarin, antidiabetic agents, calcium channel blockers, diuretics	Avoid long-term use. Prefer topical steroids.
Thiopurine	Moderate-severe UC dependent/resistant to steroid therapy	History of recent malignancy	Allopurinol Warfarin	
AntiTNF agents	Induction/maintenance of remission in moderate-severe UC	History of congestive heart failure (NYHA III-IV) and recent malignancy (< 2 years)		
Anti-integrins	Induction/maintenance of remission in UC			

Table 3. UC medical therapy

Amino Salicylates

Amino salycilates are first line therapy for induction and maintenance of remission in mild-moderate UC. Several formulations are approved, and combination of oral and topical therapy is associated with higher rate of remission than oral therapy alone [37].
Topical therapy alone may be effective in proctitis and left sided UC [37]. Despite this, this formulation doesn't fit to patients with anorectal dysfunction and fecal incontinence, which are more frequent in elderly patients. Reducing volume enema can improve adherence [13,31,38].
Aminosalicylates have a good safety profile. Caution should be used in patients with renal failure, as 5-ASA half-life could be

increased due to reduction in glomerular filtration and renal clearance. For this reason, renal function should be monitored in patients with pre-existing renal impairment and/or concomitant use of nephrotoxic drugs [27]. Other studies suggest that renal damage could be idiosyncratic rather than age-related [39].
To increase adherence, once-daily subministration should be performed [18].
Main drug interactions are represented by warfarin [40]. digoxin, hydralazine, anti-tuberculosis drugs [41]. six thioguanine (increased risk of myelosuppression) [42].

Corticosteroids

Corticosteroids represent the main therapeutic strategy for induction of remission in patients with inadequate response to aminosalicylates or with severe UC. Thus, they are not recommended as maintenance therapy because of their safety profile [37]. Some side effects typical of steroid therapy are amplified in the elderly, due to pre-existing comorbid condition, drug interactions and decreased renal and hepatic clearance. Most frequent side effects are worsening of diabetes, hypertension (as a consequence of increased fluid retention), osteoporosis (increased risk of fractures), depression/neurological disease (delirium, psychosis, hallucinations), cataracta/glaucoma, infections (in particular, patients exposed for more than 6 months) [43,44,45,46]. gastrointestinal haemorrage if used with NSAIDs, antiplatelet or anticoagulant agents [41].

In a recent meta-analysis of population-based cohort studies, cumulative 1 and 5-year risk of exposure to corticosteroids in elderly-onset UC was 40,9% (95% CI, 39,4-42,5) and 57,2% (95% CI, 0,91-1,06), with a risk of exposure to corticosteroids comparable with adult-onset UC [47].

Topical steroid use should be preferred in elderly (modified-released multimatrix system) [26].

Caution should be used in patients with hypertension and diabetes. Main drug interactions are represented by phenytoin, phenobarbital, rifampicin and warfarin, antidiabetic agents, calcium channel blockers, diuretics [17,26].

Immunomodulators

Immunomodulators are approved in moderate-severe UC dependent/resistant to steroid therapy. In elderly-onset UC, azathioprine and 6-mercaptopurine are the immunomodulators most frequently used, while methotrexate use is controversial and not enough evaluated in literature even in adult patients [27].
Therapy with immunomodulators is less used in elderly patients with UC because of risk of severe adverse events and need of blood test monitoring.

Most frequent adverse events related to azathioprine and 6-mercaptopurine use are leucopenia, nausea, dyspepsia, acute pancreatitis, transaminase increase, allergic reactions, opportunistic infections, non-melanoma skin cancer, non Hodgkin's lymphoma (in male older than 60 years). These events are more common if thiopurine are used in association with other immunosuppressant agents, such as steroid therapy or biologic drugs [48,49,50].

In IBD patiens, Lemaitre et al [51]. found that thiopurine ([aHR], 2.60; 95% CI, 1.96-3.44; p <0.001) or antiTNF monotherapy (Ahr 2.41; 95% CI, 1.60-3.64; p < 0.001) was associated with increased risk of lymphoma. This risk rises significantly in case of combination therapy (aHR 2.35; 95% CI, 1.31-4.22; p <0.001; if we consider thiopurine monotherapy) and (aHR 2.53; 95% CI, 1.35-4.77; p <0.001).

Dose adjustment should be provided in case of concomitant drug intake.

For example, in case of concomitant allopurinol use, thiopurine dose should be reduced and liver function should be monitored. Besides, warfarin activity is increased by concomitant azathioprine use [17].

Caution should be used with patients with history of recent malignancy. These patients have a higher risk of lymphoproliferative disorders, related to UC duration and to thiopurine exposure.

Ciclosporin is a rescue therapy in severely active ulcerative colitis. Adverse events related to its use are: viral warts, gram negative sepsis [52]. worsening of hypertension, nephrotoxicity if used with other nephrotoxic drug, such as trimethoprim, ciprofloxacin, gentamicin and NSAIDs.

Because of its narrow therapeutic window, ciclosporine levels can be influenced by other drugs that can inhibit P-450 cytochrome [18].

Immunomodulators should be used carefully in elderly patients with UC, particularly in case of multimorbidity and polypharmacy.

Anti-TNF

Anti-TNF agents are approved for induction and maintenance of remission in moderate-severe UC [13]. They also reduce hospitalization and risk of surgery.
In elderly-onset UC, antiTNF agents are less used, and their efficacy seems to be lower, with a higher rate of therapy discontinuation at 12 months [53].

Because of their safety profile, they are rarely used in elderly patients (1-2% older UC). Most frequent adverse events are infections, exacerbation of congestive heart failure, skin reactions, infusion reactions [10,11,13].

When this therapeutic choice is pursued, antiTNF agents should be used in monotherapy, as combination therapy amplifies risk of infections.

Caution should be used in elderly patients, especially if they present congestive heart failure (NYHA III-IV) [54]. and history of malignancy (< 2 years) [55,56].

Anti-integrins (vedolizumab)

Vedolizumab is approved for induction and maintenance of remission in UC [37]. Its gut specificity and low adverse event rate are very encouraging for elderly patients [12]. In GEMINI trials, patients > 55 years old had lower incidence of serious infections and adverse events requiring hospitalization, and no differences in malignancy or deaths [57].
A cohort study of elderly IBD patients comparing vedolizumab with antiTNF therapy found a lower but not statistically significant rate of infection after 1 year therapy (17% vs 20%), and no significant differences in rates of gastrointestinal infections (18% vs 21%) [58].

Other Biologic Agents

Ustekinumab [59]. and JAK-inhibitors (tofacitinib) have been recently approved for induction and maintenance of remission in UC [60,61].

Data in the elderly are very poor. Tofacinitib seems to be associated with an increased rate of herpes zoster infection (not EBV or CMV) in patients with concomitant steroid use [62]. worsening of dyslipidemia [63]. and higher risk of cardiovascular events and pulmonary embolism [53,64].

Caution should be used in elderly patients with a history of pulmonary embolism, deep vein thrombosis or coagulation abnormalities [65].

Surgery

Surgery is more frequently performed in the elderly [66].
Indication to surgery is similar to young patients: failure to medical therapy or complications [7].

Most frequent procedure performed is proctocolectomy with ileo-anal pouch anastomosis, with similar rates of pouch failure if compared to younger patients [12,25]. If patients are not fit for this kind of surgical technique, total colectomy with permanent ileostomy may represent a valid option, due to frequent concomitant presence of anal dysfunction and/or fecal incontinence.

Patients with elderly-onset ulcerative colitis have a higher risk of colectomy with 90 days than patients who received UC diagnosis at a younger age (3,1% vs 1,6%) [67]. In addition, 19% of old patients vs 13% of adults undergo UC-related surgery within 10 years from diagnosis [21].

Elderly patients have a longer hospitalization, surgery-related complications [68]. higher risk of infections and deep vein thrombosis [66].

Poor outcome is related to comorbidities, nutritional status and general health conditions, which should be taken into account when therapeutical approach is defined.

Malignancy

Patients with ulcerative colitis have a higher risk of developing colorectal cancer [69].
Risk factors for colorectal cancer onset are long-standing ulcerative colitis (as a result of chronic inflammation), family history of colorectal cancer, presence of primary sclerosing cholangitis and chronically active ulcerative colitis [70].

Patient with elderly onset UC have the same risk of developing colorectal cancer than adults, despite time for colorectal cancer onset tends to be shorter [6].
Most frequent extraintestinal cancers are lymphoproliferative and myeloproliferative disorders, non-melanoma skin cancer, urinary tract malignancies, as a consequence of immunosuppressant therapy, in particular thiopurine use [22,71].

Infections

Old age is an independent risk factor for infection development [72].

Elderly patients have a higher risk of serious and opportunistic infections, 2-3 times greater than younger population [73]. This is a consequence of immunosenescence and of some UC specific drugs [74].

Most common infections are pneumonia, sepsis and candidiasis. In patients on immunosuppressive therapy, risk of opportunistic infections should be considered, as viral and mycobacterial infections have been reported [74].

Mortality

Mortality is more frequent in the elderly [15,25]. Diagnostic delay increases risk of disease-related complications. Other reasons accounting for worse prognosis are comorbidities, multiple drug use (increased risk of adverse event), therapeutical limitations, poor adherence to therapy and worse post-surgery outcome per post-operative complications (cardiac and renal dysfunction, neurologic complications, infections, malignancies).

Malignancy (22%), cardiovascular disease (17%) and infections (4%) [21,34]. represent the most frequent cause of death.

Conclusion

Inflammatory bowel diseases, particularly ulcerative colitis, are more and more frequent in elderly population.

Symptoms and disease location at UC diagnosis present some differences if compared with adult age. These aspects, combined with a myriad of conditions which mimic UC clinical presentation, can make differential diagnosis challenging.
Thus, presence of comorbidities and multiple drug intakes limit/contraindicated some therapeutical strategies commonly approved for UC.

Elderly UC patients are more likely to be hospitalized and to undergo surgical intervention. Immunomodulators and biologic agents are less used, because of their higher rate of adverse event in the elderly.

It is becoming more and more clear that elderly patients cannot be considered a unique identity. Distinctions should be made between fit and frail elderly because of higher risk of drug related adverse event, infection, hospitalizations and surgery with related complications.

List of abbreviations

CD: Crohn's disease
UC: ulcerative colitis
IBD: inflammatory bowel disease
NSAID: nonsteroidal anti-inflammatory drug

Declarations

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Authors' Contributions

Study design and idea: CR, FL
Data acquisition: IZ, FL, CR
Analysis of data: IZ, FL, CR
Writing of manuscript: IZ, FL, CR
Revision of manuscript: CR, FL
All authors have read and approved the manuscript in the current state.

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