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REVIEW

Elderly patients and inflammatory bowel disease

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Abstract

The incidence and prevalence of inflammatory bowel disease (IBD) is increasing globally. Coupled with an ageing population, the number of older patients with IBD is set to increase. The clinical features and therapeutic options in young and elderly patients are comparable but there are some significant differences. The wide differential diagnosis of IBD in elderly patients may result in a delay in diagnosis. The relative dearth of data specific to elderly IBD patients often resulting from their exclusion from pivotal clinical trials and the lack of consensus guidelines have made clinical decisions somewhat challenging. In addition, age specific concerns such as co-morbidity; locomotor and cognitive function, poly-pharmacy and its consequences need to be taken into account. In applying modern treatment paradigms to the elderly, the clinician must consider the potential for more pronounced adverse effects in this vulnerable group and set appropriate boundaries maximising benefit and minimising harm. Meanwhile, clinicians need to make personalised decisions but as evidence based as possible in the holistic, considered and optimal management of IBD in elderly patients. In this review we will cover the clinical features and therapeutic options of IBD in the elderly; as well as addressing common questions and challenges posed by its management.

Key words: Inflammatory bowel disease; Crohn's disease; Ulcerative colitis; Elderly; Therapy; Clinical features

Core tip: Inflammatory bowel disease can be misdiagnosed as its clinical features are similar in younger and elderly patients. Therapeutic regimes may be different with elderly patients being less likely to have immunosuppressant drugs and Anti-TNF's either driven by clinican or patient preference and disease related factors. Important factors such as polypharmacy and co-morbidity must also be considered when making clinical decisions. Finally, complications may be more common in the elderly. Further evidence through clinical trials and consensus guidelines are needed to

assist clinicians in making evidence based decisions in these patients.

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INTRODUCTION

The inflammatory bowel diseases (IBD) comprising Crohn's disease (CD) and ulcerative colitis (UC) are idiopathic diseases of the gastrointestinal tract characterized by a relapsing and remitting course[1]. The incidence and prevalence of IBD is increasing worldwide[2,3]. An official consensus estimated the proportion of elderly people at 3%-17.8% of the population[4]. Individuals aged over 65 years represent the fastest growing age group and is expected to increase by 31% during this decade in the United States[5]. The rising global incidence of IBD, its negligible impact on mortality and an ageing population will all contribute to increasing numbers of "elderly" patients with IBD.

The challenges posed by clinical co-morbidity, poly-pharmacy and drug interactions, likely mismatch between chronological and biological age (functional status) and social issues underpin the complexities involved in the management of the elderly patient with IBD. No consensus guidelines currently exist to guide the management of this vulnerable group, often limited by heterogenous populations studied with differential definitions of endpoints and based on 8-52 wk duration studies, which are not truly reflective of a lifelong disease. Patients over 65 years are often excluded from therapeutic trials[6] and in some the median age of participants has been in the 30's with few being elderly[7]. The paucity of clinical data compounded by the complexities in management emphasise the importance of an astute understanding of the available literature in compressing avoidable morbidity and achieving desired outcomes when treating elderly patients with IBD.

In this review we will address common questions and challenges posed by the management of elderly patients with IBD. As is widely accepted in the IBD literature, we have used age 60 years and above for this cohort of patients.

EPIDEMIOLOGY OF ELDERLY IBD

Although the peak incidence of IBD is between ages 20 to 39, a second peak is recognised between ages 50-70[8]. Individuals over the age of 60 contribute to 10%-15% of IBD diagnoses, compared to 5%-25% made in children or adolescents[8-11]. The incidence in the elderly decreases with increasing age, where 65% of patients are aged 60-70 years old, 25% aged 70-80 years and 10% are over 80 years[6]. Thus, it is important to recognise elderly patients with IBD as having either long-standing IBD or late-onset IBD, where a diagnosis is made at a later age.

The incidence of IBD is increasing world-wide although there is significant heterogeneity with some data coming from urban populations and others from large population-based registries[12]. Previous studies have also shown regional differences, with the incidence of CD and UC in the elderly being 4/100000 and 6-8/100000 respectively in the United States as compared to 8-10/100000 for UC and CD in Europe[13,14]. A large study investigating early-onset IBD from the EPIMAD registry in Northern France, suggests the percentage of late-onset IBD is on the rise at 5%-11%[15]. It is noteworthy that most epidemiological studies have been undertaken in Caucasian populations and in the "developed" world. Population ageing, however, is a global phenomenon and further epidemiological studies in the developing world including the elderly may help to unmask likely clues from the "exposome" in the aetiology of IBD[16].

CLINICAL PRESENTATION OF IBD IN THE ELDERLY

The clinical presentation is similar to that in younger individuals with some important differences (Table 1). The diagnosis may be delayed for reasons including access to specialist healthcare, disinclination to seek medical advice, an initial misdiagnosis compared to younger patients, and the higher prevalence of conditions mimicking IBD in the elderly[17]. Symptoms include weight loss, abdominal pain, anaemia and diarrhoea[17-19]. Elderly patients have a lower incidence of a family history of IBD and higher incidence of osteoporosis but the extent of extra-intestinal features is not significantly different to that in younger patients[17,18].

The diagnosis of CD may be delayed in older individuals with the mean time of diagnosis being 6.4 years compared to 2.4 years in younger people[17]. Elderly CD patients have more colonic involvement and inflammatory disease compared to younger patients with a lower frequency of fistula or strictures[17-21]. A change in disease behaviour is also less common in the elderly[21-23].

The first flare of UC may be more severe[7,24-26]. However, the clinical presentation of UC may be subtle with less bleeding, diarrhoea and abdominal pain[25]. Distal disease (proctitis and left-sided colitis) is more common[21,25-27]. In a World Gastroenterology Organisation survey, proctitis was observed in 42% of UC patients aged over 60 years as compared to 33% in those under 60 years[24]. In the EPIMAD registry,

Table 1 Phenotypic characteristics of inflammatory bowel disease in elderly-onset inflammatory bowel disease

	Crohn's disease	Ulcerative colitis
Location	Colonic or ileo-colonic	Left sided or extensive disease more common than isolated proctitis
Symptoms	Less bleeding and abdominal pain than younger patients	Less diarrhoea, abdominal pain and weight loss than younger patients
Disease behaviour	Inflammatory; less progression to penetrating and structuring disease	More likely to remain stable
First episode	More severe than in younger patients	More severe than in younger patients
Extra-intestinal manifestations	Less common than in younger patients	Less common than in younger patients
Family history	Less common	Less common
Cancer risk	Higher risk of non-Hodgkin lymphoma with thiopurines and of non-melanoma skin cancer with anti-TNF therapy	Higher risk of non-Hodgkin lymphoma with thiopurines and of non-melanoma skin cancer with anti-TNF therapy

45% had left-sided colitis, 29% had proctitis and 26% had extensive colitis[15]. Furthermore, disease location tended to remain stable with only 16% of patients at follow-up having proximal disease extension[15]. Studies have suggested that relapse in UC is less likely in elderly patients but when it does occur, it may be more severe[27-29]. The incidence of colectomy is higher in younger patients (1.9% *vs* 4.3% in older and younger patients)[21]. In the EPIMAD study only 16% of elderly onset UC had surgery 10 years after diagnosis[15].

Elderly patients tend to be hospitalised more often than younger patients. Ananthakrishnan *et al*[30] reported that 25% of all IBD-related hospital admissions in the United States were in patients aged over 65 years. These patients are more likely to be ill, more malnourished, anaemic and hypovolaemic with higher transfusion requirements, and longer post-operative hospital stay especially when they undergo surgery. The majority of the healthcare spend associated with IBD relates to the cost of hospitalisation and surgery[30-32]. Increased age is an independent risk factor for hospital fatality in these patients[30,33-35]. The worse outcomes in hospitalised elderly IBD patients, higher mortality and economic impact from health resource utilization underpin the need for further prospective research into the natural history and well-designed clinical trials for therapy in this population.

Finally, thrombotic complications are more common in elderly IBD patients potentially driven by a combination of disease related hypercoagulability, reduced mobility and dehydration, all of which are more common in the elderly[17,36]. In the Nationwide Inpatient Sample Cohort Study, the highest rates of venous thromboembolism were seen in elderly UC patients with a third aged 80 and above experiencing a venous thrombotic complication during hospitalization[30].

DIFFERENTIAL DIAGNOSIS

A wide range of conditions can mimic IBD often delaying a decisive diagnosis or leading to an erroneous diagnosis. Misdiagnosis may occur in up to 60% of elderly patients with IBD as compared to 15% of younger patients with a lag in diagnosis of up to 6 years[18]. Conditions commonly confused with IBD in this age group include complicated diverticular disease (diverticulitis and diverticular bleeding), ischaemic colitis, medication-associated diarrhoea (NSAIDs, antibiotics and others), infectious diarrhoea, radiation colopathy and microscopic colitis (Table 2).

Diverticular disease is present in 40%-60% of individuals aged 70 and above with diverticular bleeding being the most common complication to mimic IBD[37]. Abscess formation, perforation or indeed fistulisation may complicate differentiation between diverticultis and CD. Furthermore, diverticular colitis (also called segmental colitis associated with diverticula) can mimic distal colonic CD[38]. A recent Dutch study found that 8% of all IBD diagnoses had been inaccurate and were indeed segmental colitis associated with diverticular disease[39].

Radiation for gynaecological or prostate cancers and NSAID-induced ulcers with strictures or perforation can mimic or complicate IBD[28,40]. Some studies have reported relapses in patients with IBD with non-selective NSAID use but not with selective COX II inhibitors[41].

Ischaemic colitis may also occur with segmental involvement causing confusion with CD. Abrupt onset of pain with bloody diarrhoea is suggestive of this diagnosis. Endoscopy, histopathology and in some instances imaging make it possible to differentiate it from CD[42]. Brandt *et al*[43] found that nearly 50% of their patients had been misdiagnosed with IBD and actually had ischaemic colitis.

Infectious colitis with bloody diarrhoea may often be confused with UC and a broad differential diagnosis must be considered, particularly *Clostridium* difficile infection (CDI), *Shigella*, *Campylobacter*, *Salmonella* and *Escherichia coli* 0157:H7. The acute onset of symptoms and associated fever is characteristic and the diagnosis is often made by stool culture with rapid symptom resolution within 1-2 wk. Infections causing

Table 2 Differential diagnosis of inflammatory bowel disease

Disease	Clinical characteristics	Additional features
Segmental colitis associated with diverticulosis	Diarrhoea with bleeding Abdominal pain	Segmental peridiverticular distribution Rectum and proximal colon spared
Radiation colitis	Diarrhoea with bleeding and abdominal pain/cramps Proctitis (urgency and tenesmus) Symptoms often weeks to years after abdominal or pelvic radiation	Telangiectasia and fibrosis seen at histology
NSAID-induced colitis	Diarrhoea with recurrent abdominal pain Obstruction or perforation Iron deficiency anaemia	Lesions isolated Any part of intestine may be affected Diaphragm like small bowel strictures Exacerbate existing CD or UC
Ischaemic colitis	Sudden onset of abdominal pain Diarrhoea with bleeding	Segmental distribution of colitis Typically sigmoid/left sided colitis Rectum spared and abrupt cut off with non-involved segment
Infective colitis	Diarrhoea with bleeding Constitutional symptoms such as fever	Possible pseudomembranes with *Clostridium* difficile colitis Stool cultures usually diagnostic Rapid resolution with appropriate antibiotic therapy
Solitary rectal ulcer	Bleeding per rectum with straining	Mucosal thickening Crypt architectural distortion Collagen deposition and smooth muscle in lamina propria

NSAID: Nonsteroidal anti-inflammatory drug; CD: Crohn's disease; UC: Ulcerative colitis.

chronic diarrhoea include *Plesiomonas*, *Aeromonas* and *Yersinia*. *Yersinia* may cause terminal ileitis mimicking CD[44]. The rising incidence of CDI is of increasing concern, and is no longer regarded as a purely nosocomial infection but can also be community-acquired[45]. In older patients affected with a virulent strain this may have serious consequences with prolonged hospitalization, increased risk of surgery and greater mortality[45]. Specific risk factors for CDI in patients with IBD are colonic disease, corticosteroid therapy and the use of immunosuppressive drugs to control IBD[46]. Thus, CDI testing should be performed on all hospitalised patients with IBD, those experiencing a disease flare and those not responding to therapy[46].

MEDICAL THERAPY

General considerations

The principles of IBD treatment are the induction and maintenance of remission, prevent disease and treatment-related complications and to improve quality of life. Important considerations in choosing a therapeutic agent include location and severity of inflammation, disease behaviour (inflammatory, stricturing or fistulising), the presence of extra-intestinal manifestations and other clinical co-morbidities. In that respect, the therapy for IBD in the elderly is similar to that in younger patients but with some crucial considerations.

Elderly-onset IBD is usually not associated with disease progression[6,21-23]. Treatment paradigms have evolved often involving the use of highly potent immunosuppressive therapy (often in combination) earlier in the disease course in well selected patients, especially in CD[47,48]. The application of such treatment paradigms in the elderly, through extrapolation from clinical trial data must acknowledge important caveats discussed below.

Innate immune function declines with age. Ageing is associated with a reduction in Toll-like receptor 4-mediated pro-inflammatory cytokine production and mitogen-activated protein kinase expression[49-54]. Ageing also alters humoral immunity through decline in B cell precursors and consequent decline in immunoglobulins[55]. Malnutrition also accentuates decline in immune function[56,57].

Treatment of elderly IBD patients with immunosuppressive medication increases the risk of opportunistic infection and possibly even malignancy. The exclusion of patients older than 60 years from most therapeutic trials[6] and lack of drug efficacy trial data in older patients, coupled with a lack of clarity of appropriate clinical end points (objective *vs* symptom control) may limit evidence-based decision-making.

Polypharmacy is common in elderly patients with some studies showing that they may be on five medications on average and 25% regularly take more than six drugs[58,59]. Thus, choice of drug therapy must take into account clinical co-morbidity, drug interactions and also the impact of polypharmacy on treatment adherence, which itself will impact on clinical outcomes[60] (Table 3). Age-related conditions, home circumstances, the influence of impaired mobility or memory and consequent need for practical support require careful attention.

Aminosalicylates

5-aminosalicylates are foundational therapy for the induction and maintenance of remission in UC[61]. Their role in CD is conflicting though patients with Crohn's colitis may benefit[62]. Despite this, in the EPIMAD study

Table 3 Drug interactions of medications used in the treatment of inflammatory bowel disease relevant to elderly patients

IBD drug	Drug interaction
Aminosalicylates	Increase levels of thiopurine metabolite 6-TGN through weak TPMT inhibition
	Interact with warfarin and increase INR (particularly Olsalazine)
Metronidazole	Increases levels of: Simvastatin; Calcium channel blockers; sildenafil and lithium
	Antabuse (disulfuram) like reaction with ethanol
	Increased metabolism and consequent clearance when co-administered with phenytoin and phenobarbitone
	Potentiates Warfarin: May increase INR
Ciprofloxacin	NSAIDs: Risk of seizures may be increased
	Theophylline: Levels may increase
	Potentiates Warfarin: May increase INR
	Phenytoin: Levels of phenytoin may decrease
Corticosteroids	Antidiabetic agents: Hypoglycaemic effects may be decreased
	Calcium channel blockers: May increase corticosteroid levels
	Diuretics: Hypokalaemic effects increased
	Warfarin: May increase anticoagulant effects
Thiopurines	Allopurinol: Can lead to bone marrow toxicity
	Aminosalicylates: May lead to increased toxicity and cause leukopenia/myelosuppression
	Clotrimazole, angiotensin–converting enzyme inhibitors: increased risk of leucopenia
	Warfarin: Anticoagulant effect may decrease
Methotrexate	Loop diuretics: Can alter methotrexate concentrations and vice versa
	NSAIDs: Bone marrow suppression and gastrointestinal toxicity
	Penicillins: Increase methotrexate concentration
	Tetracyclines: Increase methotrexate toxicity
	Theophylline levels may be increased
Cyclosporine	Ciprofloxacin, gentamicin and vancomycin: Potentiate renal dysfunction
	Anti-inflammatory drugs and histamine-2 blockers: Potentiate renal dysfunction
	Azithromycin, clarithromycin: Increase cyclosporine levels
	Allopurinol: Increases cyclosporine levels
	Rifampicin: Decreases cyclosporine levels
	Phenytoin, phenobarbital and carbamazepine: Decrease levels of cyclosporine
	Grapefruit juice: Increases absorption of cyclosporine

IBD: Inflammatory bowel disease; NSAIDs: Nonsteroidal anti-inflammatory drugs; 6-TGN: 6-thioguanine nucleotide; TPMT: Thiopurine S-methyltransferase; INR: International normalised ratio.

nearly 80% of patients with late-onset CD were prescribed a 5-ASA, possibly a reflection of physician hesitancy with immunosuppressive therapy[15].

In UC, combined therapy with oral and topical 5-ASA is more effective than oral therapy alone[63,64]. Complex dosing regimens and polypharmacy may negatively influence compliance and once-daily dosing regimens may be preferable[65]. Adherence rates of 5-ASA's are 40%-60% based on self-reporting and urinary drug measurements[66]. Anal sphincter incompetence ranges between 10% to 25% in hospitalised patients and 4% in outpatients[67]. Difficulties with the use of topical therapy may arise from physical limitations with reduced retention of enema fluid in the presence of active inflammation. Reduction in volume of the enema or substitution with a corticosteroid foam preparation may circumvent this problem.

5-aminosalicylates are relatively safe and effective with reports of nephrotoxicity and interstitial nephritis being rare[61,68]. Interstitial nephritis, an idiosyncratic effect is unrelated to the duration or dose of 5-ASA. Common negative side effects include nausea, vomiting abdominal pain, headache and rash[64]. Paradoxical worsening of colitis can occur in just under 5% of patients, and improves after discontinuing the drug[69,70]. 5-aminosalicylates can increase levels of the thiopurine metabolitie 6-thioguanine[71-73]; interact with isoniazid[58], and warfarin (particularly olsalazine) when an increase in the international normalised ratio (INR) occurs[14,74].

Antibiotics

The role of antibiotics in the primary treatment of CD is debatable but they may be used in some patients with mild - moderate colonic CD, infectious complications of fistulising CD, pouchitis and as an adjunct to surgical drainage of CD related abscesses[75]. They do not have an important role in UC, but have been used in the expectant management of fulminant colitis[76,77]. Metronidazole and ciprofloxacin are commonly used in IBD, often in combination.

Adverse effects of metronidazole include nausea, a metallic taste and neuropathy with longer use[14,78,79]. Inhibition of cytochrome P450 may lead to increased levels of HMG-CoA reductase inhibitors such as simvastatin, sildenafil and calcium channel blockers[79]. Metronidazole may affect warfarin thus prolonging the INR[14,74,79]. Patients should be advised to avoid alcohol due to the well-recognised Antabuse (disulfuram) like effect. The metabolism of metronidazole is increased when used with phenytoin. Concomitant use may

increase the risk of lithium toxicity[79].

Ciprofloxacin decreases theophylline clearance and can cause central nervous system adverse effects including lowering of the seizure threshold; it may alter serum phenytoin levels and lead to an increased INR by increasing warfarin levels[80]. Elderly patients may be at particular risk of QT prolongation on ECG and Achilles tendon rupture[81]. The association of fluoroquinolones and Clostridium difficile colitis is of particular concern[82].

Corticosteroids

Corticosteroids are used to induce remission in UC with an inadequate response to 5-ASA, in acute severe UC and to induce but not maintain clinical remission in CD[83,84]. Elderly IBD patients with prolonged corticosteroid exposure are more likely to experience severe adverse events[85,86]. Dose related side effects were noted in 40% of elderly patients with long-term corticosteroid exposure and osteoporosis in 16% of patients[85]. Another study found osteoporotic-related fractures and osteonecrosis in 15% of elderly IBD patients[87]. Corticosteroids should be used in an appropriated manner in both dose and duration with careful contingency planning[88]. The wide prevalence of malabsorption and calcium and vitamin D deficiency in the elderly emphasises the importance of early and regular bone densitometry assessments. Bisphosphonates should be considered alongside vitamin D and calcium supplementation[89].

Other side effects of corticosteroids more pronounced in the elderly include altered mental state and depression[85,86], fluid retention, of particular significance in patients with underlying hypertension, congestive heart failure, diabetes and renal disease[85,86]. Older patients may also have ocular problems such as glaucoma, exacerbated by corticosteroids[85,86]. Corticosteroid clearance is decreased in the elderly[90]. The activity of drugs can be reduced, such as phenytoin, phenobarbital, ephedrine and rifampin due to an increase in corticosteroid metabolism[14]. Anticoagulant efficacy may also be affected and frequent checks of coagulation parameters are recommended[58].

Budesonide is recommended to induce remission in mild-to-moderate distal small bowel and right-sided colonic CD and affects bone metabolism less than conventional corticosteroids[90,91]. A novel formulation of Budesonide in a multi-matrix release formulation has been approved for use in mild-moderate extensive UC[91].

Immune modulator therapy

Immunomonthsdulator therapy may be indicated in elderly patients with aminosalicylate resistance or corticosteroid dependence for the maintenance of remission. Thiopurines (azathioprine and 6-mercaptopurine) are useful in the preservation of remission in CD and UC whereas intramuscular methotrexate has efficacy in moderate to severe CD[64,92]. Although the efficacy of immune modifying agents in elderly and younger IBD patients appears similar, the literature is disparate with one study showing no differences in uptake[93], and another demonstrating higher immunosuppressive therapy use secondary to corticosteroid dependence[94]. In contrast, in a retrospective study of 393 IBD patients aged over 65 years, a third were on long-term corticosteroids (treatment duration over 6 mo) with only 6% on thiopurines (azathioprine or 6-MP) and 1% on Methotrexate indicating underutilization[22].

Adverse events associated with thiopurine therapy include idiosyncratic reactions that develop in approximately 5% of patients and include: Fever, pancreatitis and hepatitis[95]. Leucopenia may occur at any time during therapy and is determined mainly by activity of the enzyme thiopurine methyltransferase (TPMT), which metabolises azathioprine to its metabolite 6-thioguanine. TPMT deficiency can result in serious leucopenia and mandates vigilant monitoring of blood counts and chemistry particularly as the incidence of serious infection in the elderly is greater[94-98]. TPMT testing (enzyme activity or genetic) prior to initiation of thiopurine therapy can identify those at risk of serious myelosuppression[99,100]. TPMT deficiency is not the only mechanistic explanation for thiopurine-induced myelosuppression and vigilant blood count monitoring is mandated in all patients[101]. Thiopurines are also associated with an increased risk of non-melanoma skin cancer and patients should be counselled regarding appropriated exposure to sunshine with adequate precaution using barrier sun creams and an annual dermatological assessment[102].

Bone marrow toxicity can occur when thiopurines are used with allopurinol. In such instances, the thiopurine dose should be reduced to 25% of the standard dose[73,103,104]. Using both immunomodulators and allopurinol also increases the incidence of infection in the elderly[103,104]. The risk of leucopenia is also increased when thiopurines are used along with with clotrimazole or angiotensin-converting enzyme inhibitors[103,104]. Thiopurine treatment increases the risk of non-Hodgkin's lymphoma, its duration, age and if used with TNF therapy[105-107]. The CESAME study identified older age, male sex and longer duration of disease as the main risk factors of developing lymphoma[107]. Of 23 patients diagnosed with incident lymphomas, 12 were aged 60 or above and the risk was further elevated in those on combined immunosuppressive therapy with thiopurine and anti-TNF agents[107].

Methotrexate

Methotrexate is used in the treatment of CD but consensus opinion does not currently recommend its use in UC[108,109]. Although it has not been studied specifically in the elderly there is experience with its use in older patients with psoriasis and rheumatoid

arthritis[110,111]. The efficacy is similar in younger and older patients although its metabolism through biliary and renal excretion may be affected by age[112].

NSAID's may inhibit renal excretion, increasing toxicity[112]. Gastrointestinal and haematological toxicity are also more likely in older patients[112]. Common side-effects may include nausea, fatigue, rash and stomatitis but also using folic acid supplements can prevent or reduce these[113]. Other clinically relevant drug interactions include inhibition of methotrexate absorption by tetracycline and reduction in renal clearance by penicillin. Methotrexate alters theophylline clearance[14]. Loop diuretics and methotrexate can alter concentrations of either drug[114]. Methotrexate does not appear to increase the risk of lymphoma[115].

Cyclosporine

Cyclosporine is sometimes used as rescue therapy in fulminant colitis but with no definite superiority over infliximab its use in modern IBD therapy is likely to be limited[116]. Elderly patients are most likely to experience side effects[66,69,117,118]. Cyclosporine can interact with antibiotics, such as gentamicin and vancomycin, leading to increased nephrotoxicity; and with NSAIDs, melphalan and histamine-2 receptor antagonists[14]. Cytochrome P450 inhibitors, such as verapamil and allopurinol, decrease the metabolism of cyclosporine and increase its serum levels[14]. Phenytoin, rifampin, carbamazepine and phenobarbital reduce cyclosporine blood levels *via* increased hepatic metabolism[14,119].

Biological therapies

The role of anti-TNF therapy in the induction and maintenance of clinical and histological remission of moderate to severely active IBD has been established through pivotal trials with evidence that it reduces hospitalisation rates and surgery and improves quality of life[64,84]. There is a lack of data demonstrating how they affect older patients. Nonetheless, indications are similar to those for younger patients[120-122].

Data on anti-TNF therapy in the elderly however are conflicting with some studies demonstrating similar results in older and younger patients[122-124] and others showing them to be less effective in elderly patients[125,126]. One study from the Massachusetts General Hospital found a lower response in older patients (61%) as compared to 83% in younger Anti-TNF treated patients[126]. A recent Belgian study however reported similar clinical response rates[123].

In the EPIMAD study between 2.5%-10% of patients with elderly onset IBD received immunosuppressive agents after 1 year. Only 26 patients with CD and 4 with UC received anti-TNF agents, which mirrors trends in other countries. This reflects relative underutilization of anti-TNF therapy perhaps driven by physician concern with adverse effects[15].

Data on biologics safety in elderly patients are predominantly from the rheumatological literature and conflicting, with some studies showing no increased risk of infection and others showing a higher rate of discontinuation owing to adverse effects[127-129]. Early experience from the Mayo Clinic demonstrated that 3 of 4 deaths due to infliximab treatment were in elderly patients. The independent contribution of age was unclear as these patients had a long disease course, more severe disease and co-morbidities[125]. Data from the Stockholm cohort study showed an increased risk of severe adverse effects and mortality in patients aged 60 years and above with severe infections occurring in 11% of elderly patients as compared to 2% in clinical trials and post marketing studies[120,130]. Notably, these patients were from a tertiary referral cohort and the control population in this study was retrospectively recruited which might lead one to speculate that patients treated with biologics may experience more serious disease and further complications[120]. Cottone *et al*[124] reported a 12% risk of serious infection when treated with biological therapy and 3% died from septic shock. Desai *et al*[126] reported that 70% discontinued biological therapy after a mean of two years.

Biological therapy has been associated with the risk of malignancy particularly lymphoma and melanoma skin cancer[131]. However, in most studies patients were prescribed concomitant immunosuppressant therapy and thus the risk of biological monotherapy is hard to extrapolate[115]. The TREAT registry, examining outcomes of CD treatment regimens in North America noted no increased risk of malignancy in patients treated with biologics as compared to other treatments. Furthermore, when compared to the background risk of other malignancies in the Surveillance, Epidemiology and End Results (SEER) database, no additional risk of malignancy was noted with biologics[62]. Long-term data are needed to define this risk.

Adverse effects relevant to clinical practice include exacerbation of congestive cardiac failure, psoriasis, infusion reactions and neurological sequelae such as demyelination[132,133]. The increase in mortality associated with exacerbation of congestive cardiac failure, a common comorbidity in the elderly population, contraindicates its use in the setting of NYHA class Ⅲ and Ⅳ heart failure[134]. Taken together these data emphasise the need for an astute clinical judgement, assessment of disease severity and careful counselling of therapy related risks.

SURGERY

Failure of medical therapy is the most likely cause for elderly IBD patients to have surgery[21,135]. Surgery associated complications and mortality have decreased significantly over the years from 50% between 1960-1984 to 20% between 1994-1999[136].

Recent studies show that there is not much difference in the risk of surgery for older and younger IBD patients[21,137,138]. Ananthakrishnan *et al*[135] reported that although elderly UC patients were less likely to undergo surgery there were similar surgical rates amongst younger and older CD patients. Factors attributable to adverse outcomes include advancing age, male gender, hypoalbuminemia and urgent surgery[22]. Clostridium difficile infection, colorectal cancer and dysplasia are more common indications for surgery in older patients.

Ileal pouch anal anastomosis (IPAA) is the surgical technique of choice in UC if the patient has good anal sphincter function and no history of faecal incontinence[83,139]. The American Society of Colon and Rectal Surgeons recommends that chronological age should not be an exclusion criterion for IPAA surgery[140]. Pouch function deteriorates with increasing age in all patients undergoing IPAA with faecal incontinence; this effect may be more pronounced in the elderly[141]. Despite this, patients report a high level of satisfaction with IPAA, with 89% of elderly UC patients stating that they would opt to undergo the procedure again and 96% willing to recommend it to others[142]. Careful patient selection, taking anal sphincter function, loco-motor and cognitive function into account could lead to favourable outcomes.

IBD RELATED COLORECTAL CANCER

Colitis-associated colorectal cancer (CAC) is one of the most feared complications of long-standing UC and Crohn's colitis. Several risk factors are associated with the development of colorectal neoplasia and include disease extent and duration, severity of histologic and endoscopic inflammation, colitis associated dysplasia, family history and primary sclerosing cholangitis[64,143,144]. Patients with subtotal colitis and pancolitis have the highest risk of developing CAC whereas those with proctitis or distal proctosigmoiditis are at no increased risk compared to the general population[64,144,145]. Patients with left-sided disease (to splenic flexure) carry an intermediate risk but their risk approaches that of patients with pancolitis as disease duration increases[145,146]. The relative risk (RR) increases after 8-10 years of disease and this is the rationale behind the initiation of surveillance colonoscopy[64,143,144,147,148].

Surveillance guidelines for the elderly are not different but need a considered approach. Elderly patients with IBD must be considered in two groups: Those diagnosed at a younger age, *i.e.,* before the age of 60 (long-standing IBD) and those with onset of IBD at a later age (late-onset IBD); with long-standing IBD conferring a higher risk of CAC[64,143,144,147,148]. Shaukat *et al*[149] using a SEER-Medicare linkage program database recently demonstrated that patients transitioning to older age with CD or UC had an OR of 1.93 ($P < 0.001$) and 1.45 ($P = 0.01$) respectively, of developing CAC thus reflecting disease duration, a risk factor for dysplasia in CAC. However, in a recent study comparing non-IBD patients over a six-year period, late-onset IBD was not associated with an increased risk of CAC[150]. This lower risk may be reflective of the shorter duration of the study although the immunobiology of CAC in older patients may be different.

The overriding principle governing colorectal cancer screening is that it should only be done in patients deemed fit to undergo colectomy should dysplasia be found and a life expectancy such that they would be expected to benefit[151]. Increasing age is an independent risk factor for complications at colonoscopy such as colonic perforation[152,153]. Careful patient selection and counselling is a key determinant to good outcomes[151].

VACCINATIONS

IBD patients treated with corticosteroids, immunomodulators and biological agents are at increased risk of developing infectious complications from immune suppression[154,155]. Elderly patients may have additional comorbidities and indeed immunosenescence makes them more susceptible to infection. Many of these diseases are vaccine preventable, yet there have been multiple case reports of infections including fulminant hepatitis and fatal varicella in IBD patients[156,157]. IBD patients are considered immunosuppressed with treatment if they are on 20 mg or more of prednisolone (or equivalent), on-going treatment with effective doses of thiopurines, methotrexate, biological therapies or indeed have had these agents discontinued within 3 mo[154]. There are no significant differences in vaccination guidelines for elderly and younger IBD patients but patients over 60 years old may have sub-optimal serological responses[154,158,159]. Recommended vaccinations include the inactivated influenza vaccine annually, pneumococcal vaccine given periodically (5-yearly), the initial dose followed by the vaccination in over 65 years after five years whether immunosuppressed or not, the hepatitis B series of vaccinations (after immunity is checked and if not immune), the meningococcal vaccine in certain instances (living in enclosed spaces such as dormitories) and those who have undergone splenectomy[154,158]. Live vaccines should be avoided in immunosuppressed patients and these typically include the intranasal influenza, BCG, typhoid oral, varicella, yellow fever, anthrax, measles mumps and rubella (Table 4). If required, live vaccines must be given at least 3 wk before commencing meaningful immunosuppressive therapy or 3 mo after stopping such therapy. Inactivated vaccines may be given at any time from the diagnosis of IBD but ideally at the earliest available opportunity after diagnosis. Recent data suggest that administration

Table 4 Live and attenuated vaccines

Live	Attenuated
Anthrax	Hepatitis B
Intranasal influenza	Human papilloma virus
Measles-mumps-rubella	Influenza
Polio oral vaccine	Pneumococcal
Small pox	
Tuberculosis BCG	
Typhoid	
Varicella	
Yellow fever	

BCG: Bacille Calmette-Guerin.

of the live herpes zoster vaccine may be safe even in patients prescribed Anti-TNF agents[159]. Clinician must carefully weigh the pros and cons of vaccinating *vs* not vaccinating, as consensus guidelines do not currently recommend live vaccinations in patients on immunosuppressive therapy[157].

FUNCTION, COGNITION AND QUALITY OF LIFE CONSIDERATIONS

An appreciation of the potential differences between chronological and biological age is vital for the holistic management of an elderly patient with IBD. Thus, the distinction between "fit and frail" will facilitate a more considered approach[28]. A frail patient with co-morbid illnesses and limited mobility would be at a higher risk of a medical or surgical intervention than a "fit" elderly patient. Health care utilisation by frail patients is notably higher and often related to multi-drug exposure, limited mobility, falls and cognitive impairment[160-166]. Data from the Nationwide Inpatient Sample showed worse outcomes from hospitalisations in elderly patients with 15.7% of patients aged 65-84 years and 35% of patients aged over 85 years requiring discharge to a nursing home or rehabilitation facility compared to less than 1% in individuals aged under 45 years. Furthermore, 12.6% of patients aged 65-84 years required home health care after discharge compared to 4.7% in those aged 18-45 years[135].

CONCLUSION

The rising global incidence of IBD and an ageing population implies that the prevalence of IBD in the elderly is set to increase. The clinical features and therapeutic options in elderly IBD patients are similar to those in younger patients but with important differences. The broad differential diagnosis and emerging patterns of phenotypic progression in the elderly, relative dearth of data specific to elderly IBD patients, their exclusion from pivotal clinical trials and the lack of consensus guidelines have made clinical decisions somewhat challenging. In addition, age specific concerns such as co-morbidity; loco-motor and cognitive function, poly-pharmacy and its consequences must all be taken into account. In applying modern treatment paradigms to the elderly, the clinician must pause to consider the potential for more pronounced adverse effects in this vulnerable group and set appropriate boundaries maximising benefit and minimising harm. There is an urgent need for more data on disease presentation and natural history, clinical trial data assessing treatment paradigms and medication safety, endoscopic complications and hospitalisation. Until then and as discussed, clinicians must make personalised decisions, as evidence based as possible in the holistic, considered and optimal management of elderly patients with IBD.

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