



## ECCO Topical Review

# European Crohn's and Colitis Organisation Topical Review on IBD in the Elderly

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## Abstract

This ECCO topical review of the European Crohn's and Colitis Organisation [ECCO] focuses on the epidemiology, pathophysiology, diagnosis, management and outcome of the two most common forms of inflammatory bowel disease, Crohn's disease and ulcerative colitis, in elderly patients. The objective was to reach expert consensus to provide evidence-based guidance for clinical practice.

**Key Words:** Crohn's disease; ulcerative colitis; European Crohn's and Colitis Organisation; inflammatory bowel disease; elderly; treatment outcome; frailty

## Introduction

The rising incidence of inflammatory bowel disease [IBD] and the growth of our ageing population are contributing to a rapidly increasing number of elderly IBD patients. About 25–35% of the IBD population is over the age of 60 years, of whom about 15% have been diagnosed relatively late in life, and about 20% are IBD

patients who have transitioned into older age with IBD having been diagnosed at a younger age.<sup>1,2</sup>

For elderly IBD patients, the disease course, treatment efficacy and possible side effects of therapy, and not least, the extent to which patients' quality of life is affected differs in comparison to younger patients. It is difficult to extract data for elderly IBD patients from clinical studies as

elderly patients are often excluded from clinical trials. The term 'elderly' is used to describe patients over 60 or 65, and in some cases over 70 years of age, and studies do not distinguish between elderly-onset IBD and elderly patients who were diagnosed at a younger age.<sup>3,4</sup>

Nevertheless, the health status of the elderly compared to the younger population is more heterogeneous in terms of the effects that ageing has on an individual's quality of life, functional limitations and the type of disease, comorbidities and conditions by which they are affected. Although health status is one of the major determinants of disability, the relationship is non-linear, and the onset and presentation of disability cannot be reliably predicted based on clinical diagnosis alone.<sup>5</sup>

#### ECCO Current Practice Position 1

The widely accepted definition of elderly-onset IBD is disease onset at an age of 60 years or older. When making management decisions in the elderly, clinicians should assess an individual's frailty, rather than only considering an individual's chronological/biological age

The European Crohn's and Colitis Organisation [ECCO] set up a topical review consensus group on the specifics of IBD in elderly patients. ECCO topical reviews result from expert opinion consensus endorsed by ECCO.

As controlled data are lacking, a topical review is distinct from the ECCO consensus guidelines and is intended to provide guidance in clinical areas where scientific evidence is rare. After an open call was announced to all ECCO members and members were selected based on their expertise in the topic, two subgroups were formed: Working Group 1 focused on differences in the clinical course and diagnosis as well as the incidence and relevance of comorbidities and co-medication, while Working Group 2 focused on differences in medical treatment, side effects of medical interventions and surgical management. The working parties performed a systematic literature search of their topic with the appropriate key words using Medline/PubMed and the Cochrane database, as well as their own files. Discussions and exchange of the literature evidence among the working party members and two preliminary voting rounds took place, followed by a revision of the statements. The working parties met in Barcelona on October 25, 2015 to agree on the statements. Statements were accepted when 80% or more participants were in agreement and were henceforth termed a *Topical Review Statement*. The group leaders and their respective working party wrote the final section for each subgroup. Statements are intended to be read in context with qualifying comments and not in isolation. The final text was edited for consistency of style by the steering committee, Andreas Sturm and Paolo Gionchetti, before being circulated and approved by the participants. In several areas, the level of evidence is generally low, which reflects the paucity of randomized controlled trials. Consequently, where appropriate, expert opinion is included.

#### Incidence in the elderly

Incidence rates for ulcerative colitis [UC] are higher than those for Crohn's disease [CD] in the over 60s almost universally and range from 1.8 per 100 000 to 20 per 100 000 in Europe and the USA, with much lower rates in the Asia Pacific region. For CD, incidence rates range from 1 per 100 000 to 10 per 100 000 in Europe to as high as 50 per 100 000 in New Zealand,<sup>6</sup> with much lower rates in the rest of the Asia Pacific region.<sup>7</sup>

Incidence rates for UC and CD peak in the third and fourth decade and decline thereafter, although a number of patterns can be discerned in this decline. For UC, for instance, amongst sizeable cohorts

in Canada,<sup>8</sup> Denmark<sup>9</sup> and northern California,<sup>10</sup> there is no decline in UC with age, whilst in other populations where there is a decline, it is most marked in women or nearly absent in men [New Zealand, Spain, France, Holland, Sweden, Hungary, Olmstead County].<sup>11–18</sup> There is little evidence from the developing world on age-specific incidence.

For CD, again, there are two patterns: in the first there is no decline of CD into old age [northern California,<sup>10</sup> New Zealand<sup>11</sup>] but in the majority of studies there is a marked decline into old age in both men and women with the latter being the more pronounced as the decline is from a higher incidence rate in young adult life.<sup>9,19</sup>

The proportion of IBD cases diagnosed in old age in each population is of practical importance, and will vary not only with the age-specific incidence rates but also with the age structure of the population. In the Danish National Cohort,<sup>9</sup> 21% of cases of UC and 17% of cases of CD were diagnosed over the age of 60. In another Scandinavian population from Stockholm County it was 18% of CD cases.<sup>19</sup> This population has one of the highest reported incidences of IBD. These figures are comparable to Liege where 22% of IBD cases were diagnosed after the age of 60.<sup>20</sup> Lower rates of 11% for UC and 4% for CD were reported from Hungary,<sup>15</sup> 11% and 5% in northern France,<sup>21</sup> and 12% and 6% in Olmstead County.<sup>16,17</sup>

There are no reports on the prevalence of IBD in the elderly, but it is likely that the elderly make up a slightly lower proportion of prevalent cases given their increased mortality from other causes.

Temporal trends in IBD in the elderly are difficult to assess, but in most countries, particularly the relatively less affluent, it is likely that the incidence will rise in the future or is currently on the rise.<sup>1</sup> In those populations with an already high incidence there is evidence of a continued rise in CD in some<sup>19</sup> but not all cohorts,<sup>18</sup> and there is also evidence that the rate of rise in UC in the elderly may be levelling off.<sup>15</sup>

#### Risk factors for IBD in the elderly

**Gender:** In general sex ratios for CD are equal in Montreal A1 disease, with a modest female preponderance in A2 with a fall to a more equal sex incidence in A3. In the Danish National cohort, the female incident preponderance was most marked in the 15–29 age group, falling to a modest preponderance of 7.9 versus 6.1 per 100 000 in the 60–74 age group.<sup>9</sup> For UC in the same cohort, an approximate equal incidence for men and women became a slight male preponderance over the age of 60. In the largest inception cohort of elderly patients, female predominance for CD prior to the menopause gave way to a more equal sex ratio following the menopause before rising to a female preponderance of 1.5:1 in the over 60s. For UC in this same cohort, male preponderance gradually increases throughout life with male to female ratios of 2:1 from 40 years onwards.<sup>21</sup> Most other cohorts replicate these observations.<sup>6</sup>

**Family history:** There is not much data specifically addressing this issue. In the EPIMAD registry, family history for CD and UC fall with age such that just 7% of CD subjects over the age of 60 had a family history versus 16% of A1 onset patients.<sup>21</sup> For UC the respective figures were 3% for elderly versus 13% in A1. Specific genetic variants such as NOD2/CARD are risk factors for early-onset CD, and as such would be expected to be less common in the elderly.

**Obesity:** Obesity is an emerging risk factor for CD, confirmed in one case control study<sup>22</sup> and two prospective population-based studies<sup>23,24</sup> but refuted in another.<sup>25</sup> The relationship may well be U-shaped. In the only study to allow assessment at older ages, obesity was more prevalent in CD mainly in subjects aged over 55, with 11/34 [32%] versus 10/64 [16%] of those with UC.

No elderly-specific data are available on the role of appendectomy or many of the other established risk factors, such as lack of dietary fibre and exercise, for CD. Other putative risk factors relating to childhood do not appear to be relevant.

In conclusion, trends in risk factors observed with age in younger age groups generally continue into old age, suggesting that old-age-onset IBD has a similar underlying aetiology to that observed in younger subjects. However, many risk factors for IBD were determined nearly exclusively in young populations. More elderly-specific data are needed to elucidate whether the underlying aetiology is similar between adult-onset and elderly-onset disease.

### Disease presentation

Some elderly patients may have atypical presentations of their disease, although the first symptoms of IBD are more or less similar for adult and elderly patients.<sup>26</sup> Abdominal pain and systemic complaints, such as fever and weight loss, are less frequently observed in elderly patients than in younger IBD patients.<sup>21,27–29</sup> In line with a more frequent colonic localization of CD, elderly CD patients more often suffer from rectal bleeding and less often report abdominal pain at first presentation.<sup>21,28</sup> Elderly UC patients are more frequently hospitalized for the first flare than younger adult patients, whereas elderly CD patients more often undergo a surgical resection at that time, in contrast to adult-onset CD patients.<sup>1</sup> These observations may be the result of either a more severe first presentation, a more difficult diagnostic process or the frailty of this patient population. The differential diagnosis is more diverse in the elderly, and one should exclude, among others, an infectious cause, ischaemic colitis, segmental colitis associated with diverticular disease or non-steroidal anti-inflammatory drug [NSAID]-induced colitis [Table 1]. Good history taking and endoscopy including the taking of biopsies are important to discriminate IBD from other diagnoses.

#### ECCO Current Practice Position 2

Elderly patients with CD tend to have more rectal bleeding and less abdominal pain, fever or weight loss at presentation. In UC, the clinical presentation is similar among age groups

#### ECCO Current Practice Position 3

Diagnostic work-up in elderly IBD does not differ from other adult patients. However, the differential diagnosis is more diverse in the elderly, and in particular malignancies, infectious causes, ischaemic colitis, microscopic colitis, segmental colitis associated with diverticular disease or non-steroidal anti-inflammatory agents use should be carefully excluded

### Disease course

Extent of disease is more limited in the elderly than in the adult population. Ileocolonic involvement [L3] in CD<sup>1,15,21,30,31</sup> and extensive disease [E3] in UC<sup>1,15,21,29,32,33</sup> are less common in the elderly population. In elderly CD patients, colonic involvement [L2] is more common than ileal involvement [L1].<sup>1,15,21</sup> In UC, left-sided disease is the most common and strict rectal disease is less common in the elderly than in the adult population.<sup>1,15,21</sup> The current literature is divided on the number of elderly with a B2 [stricturing] or B3 [penetrating] CD phenotype, ranging from less<sup>21</sup> to more<sup>15</sup> complicated phenotype at diagnosis. Progression to either B2 or B3 disease during the course of the disease is likely to occur to a lesser extent<sup>15</sup> or to the same extent<sup>1</sup> as in the adult CD population.

During the disease course, elderly UC patients have a higher risk of being hospitalized, in particular for the first flare. In CD, the IBD-related hospitalization rate was found to be similar for both adult-onset and elderly-onset disease.<sup>1</sup> Elderly IBD patients were found to have a longer postoperative stay and a higher in-hospital mortality rate.<sup>34</sup> Although elderly CD patients have a higher risk of surgery at or shortly after diagnosis, the long-term surgery rate seems to be no different from that for adult-onset disease.<sup>1,15,30</sup> For UC, no differences in surgery risk were found either at diagnosis or in the long term.<sup>1,15,32</sup> Data on the actual course of the disease [e.g. number of flares, severity of symptoms, time spent in remission] are currently lacking. This information is especially relevant to the elderly population, as treatment may be more focused on symptom control rather than on optimizing the long-term outcome.

#### ECCO Current Practice Position 4

In CD, elderly patients more often have colonic involvement [L2], rather than ileal involvement [L1]. UC disease extent at diagnosis is most often left-sided colitis, while extensive disease and isolated proctitis are proportionately less frequent than in adults

#### ECCO Current Practice Position 5

The risk of IBD-related hospitalization is higher in elderly UC, but not CD patients, than in younger adults. Elderly CD patients have a higher risk of surgery at or shortly after diagnosis, whereas the long-term surgery rate appears to be similar to adult-onset disease. For UC, no differences in risk of surgery are known

**Table 1.** Differential diagnosis of IBD at elderly age

	Symptoms	Possible discrimination with IBD
Infectious gastroenteritis	Acute onset of diarrhoea	Recent antibiotic use Stool sample for pathogenic organisms, including <i>C. difficile</i>
Ischaemic disease	Bloody diarrhoea Acute abdominal pain, associated with meal intake	Thorough cardiovascular history taking [including congestive heart failure, cardiac arrhythmias, atherosclerotic disease, embolic disease, vasculitis and diabetes] Different localization pattern
Diverticular disease [diverticulitis]	Abdominal pain Diarrhoea	History of diverticular disease Local inflammation around diverticular part of the colon during endoscopy
Microscopic colitis	Non-bloody diarrhoea Predominantly in females	No anatomical abnormalities visible at endoscopy Histologically different from IBD
NSAID-induced enteritis	Diarrhoea Abdominal pain	History of NSAID use
Radiation colitis	Bloody diarrhoea Abdominal pain	History of abdominal or pelvic radiation Histologically different from IBD
Rectal ulcer syndrome	Bloody diarrhoea	History of constipation Histologically different from IBD

## Infectious complications and vaccination

Infections in overall terms, and serious infections in particular, are more common in elderly IBD patients, especially in those receiving oral corticosteroids.<sup>35–39</sup>

Older age per se is a well-known risk factor for *Clostridium difficile* infection [CDI] and especially in IBD patients and those receiving glucocorticoids.<sup>40,41</sup> CDI is a significant cause of morbidity and mortality in IBD.<sup>42–44</sup> Urinary tract infection and sepsis are more common in the elderly and are related to higher mortality.<sup>42</sup> Risk of tuberculosis [TB] increases with age and use of anti-tumour necrosis factors [TNFs]. Every patient should be checked for TB prior to initiation of immunosuppressants or biological therapy.<sup>39</sup>

Age >50 years is a risk factor for opportunistic infections with the use of immunomodulators being a risk factor. There is an increased risk of candidiasis in patients receiving glucocorticoids. Other opportunistic infections reported include atypical bacterial infections, aspergillosis, coccidioidomycosis, legionellosis, cryptococcal infections, nocardiosis, toxoplasmosis, *Pneumocystis jirovecii* pneumonia, disseminated sporotrichosis, listeriosis and *Histoplasma capsulatum*.<sup>45,46</sup>

Patients older than 65 years treated with TNF inhibitors for IBD have a high rate of severe infections and mortality compared with younger patients or patients of the same age who did not receive this therapy. Patients receiving thiopurines have a greater risk for viral infections, including cytomegalovirus, herpes simplex virus, *Varicella zoster* virus [VZV] and Epstein–Barr virus. Advanced age is an additional independent risk factor.<sup>47</sup>

The current ECCO opportunistic infections guidelines on vaccinations and preventive measures provide global guidance and only recommendations specifically suggested for elderly IBD patients will be discussed here.<sup>39</sup> There is an increased risk of VZV infection in the elderly<sup>48</sup>—therefore all seronegative IBD patients should be vaccinated before immunosuppression [IMS] treatment.<sup>49</sup> Pneumococcal and influenza infections, the two most common infections in adults with high morbidity and mortality in patients over 65 years, can be prevented by vaccination. Patients who are over 65 years and/or immunosuppressed should receive at least one dose of pneumococcal vaccine, with revaccination after 5 years. Injectable influenza vaccine should be administered every year.<sup>50,51</sup> It must be highlighted that there are studies which support normal administration of vaccines even in thiopurine-treated IBD patients.<sup>52</sup> By contrast, other studies claim that immunomodulators impair the immune response to vaccination.<sup>53</sup> Anti-TNF therapy either alone or with azathioprine impairs response to pneumococcal vaccination<sup>53,54</sup> as well as trivalent influenza vaccination.<sup>55</sup> There are data showing a reduced immunogenicity in the IBD population and a suboptimal response to the pH1N1 vaccine in IBD patients on combination therapy compared to those on anti-TNF monotherapy and healthy controls.<sup>56,57</sup>

### ECCO Current Practice Position 6

Infections and related serious complications are more common in the elderly IBD patients, emphasizing the need to follow immunization guidelines thoroughly

## Neoplasia

There is an increased risk for colorectal cancer [CRC] in longstanding colonic IBD [either UC or CD]<sup>58–66</sup> and additionally an increased risk for small bowel carcinoma in CD patients.<sup>67–69</sup>

However, there is no clear increased CRC risk with advancing age itself.<sup>70–73</sup> In the case of late-onset IBD, the data are sparse. A study from Oslo published in 2009<sup>74</sup> claims that higher age at onset of IBD

may be related to a more aggressive development of CRC in IBD and suggests considering early inclusion in screening programmes. More specifically, the authors claim that the colitis–CRC interval is decreased by a factor of 0.154 when age is increased by 1 year. Baars *et al.*<sup>75</sup> also showed that IBD diagnosis at older age is related to earlier CRC and suggest possibly intensifying surveillance. A low incidence of CRC and relatively high rate of post-procedure hospitalization were found among elderly patients undergoing surveillance colonoscopy. Recommendations for ongoing surveillance in the elderly population should take into consideration the impact of comorbid illness and increasing age on the anticipated risks and benefits of colonoscopy.<sup>76</sup>

Regarding previous cancer and IBD, Beaugerie *et al.*<sup>77</sup> suggested that 2 years should pass between the completion of cancer treatment and the initiation of IMS. Special caution is indicated for non-melanoma skin cancer and high-grade cervical dysplasia—relative contraindications to IMS. There is a study that proposes methotrexate as the best choice for patients with cancer history.<sup>78</sup> The CESAME cohort indicates that IMS did not alter the rate of incident cancers.<sup>79</sup>

Lymphoma risk increases with age according to the SEER [Surveillance, epidemiology and end results] database. In a meta-analysis by Kandiel *et al.*<sup>80</sup> the risk of lymphoma in IBD patients treated with azathioprine and 6-mercaptopurine was four-fold increased. It must be noted that in the group analysis the lymphoma incidence increased from 7.65 in the age-group 20–29 to 56.45 in the age-group 60–69 and the number needed to harm from 4357 to 591, respectively. In addition, the CESAME group identified older age and longer duration of IBD as the main risk factors for developing a lymphoproliferative disorder.<sup>81</sup> Another meta-analysis from Siegel *et al.*<sup>82</sup> showed that the baseline risk of non-Hodgkin lymphoma in patients receiving biological therapies increases with age and although statistical significance was only reached for one age category (men aged 55–64 had a standardized infection ratio [SIR] of 16.8), there is a dramatic increase in the absolute rate and SIR as patients get older. The same result was published by Afif *et al.*<sup>83</sup> stating that age [per decade] [odds ratio, 1.72; 95% confidence interval, 1.38–2.14] was significantly associated with increased odds for lymphoma. A third meta-analysis by Kotlyar *et al.*<sup>84</sup> also showed increased risk in patients older than 50 years. Lewis *et al.* proved that use of azathioprine in the elderly should be avoided, as quality-adjusted life-years were increased <0.01 for patients older than 55 years.<sup>85</sup>

It should be noted that patients over 65 years who receive IMS have also increased risk for non-melanoma skin cancer.<sup>86</sup>

### ECCO Current Practice Position 7

Elderly IBD patients with longstanding disease require screening for colorectal cancer [CRC]. Elderly-onset IBD itself is not associated with an additional increased risk of CRC, although the time between the onset of IBD and CRC diagnosis is shorter in elderly patients. Therefore, one should consider enrolling elderly-onset IBD patients in a CRC screening programme sooner after IBD diagnosis. CRC screening in the elderly should be balanced with disease severity, comorbidities and life expectancy

## Medical Therapy

### General Principles

The approach to treatments and response rates to most treatments are similar in elderly patients with IBD when compared to those



with younger age at presentation or onset of the disease.<sup>36</sup> However, there are significant variations in drug prescription rates in elderly IBD patients between different countries.<sup>87</sup> Moreover, in a study of 400 elderly IBD patients, up to 32% were receiving maintenance corticosteroids but immunomodulators and biologics were used in only 6% and 3% of patients, respectively.<sup>88</sup> Data from the EPIMAD registry,<sup>21</sup> including 841 patients aged over 65 years at IBD diagnosis, showed that only 27% of CD and 16% of UC patients received immunosuppressive agents after 10 years and only 3% received anti-TNF therapy.

The use of topical therapy in elderly IBD patients presents special challenges relating to sphincter incompetence and co-ordination skills to self-administer, and these need to be considered before embarking on prescribing topical therapies.<sup>89</sup> Furthermore, elderly patients with fewer physical reserves may not tolerate a flare up of colitis as well without intensive medical treatment compared to younger patients.<sup>90</sup>

Another aspect related to drug therapy in elderly IBD patients is polypharmacy and complex regimens.<sup>91</sup> In elderly CD patients, polypharmacy was common with an average of seven drugs per patient.<sup>88</sup> This may have an impact on adherence, drug interactions and toxicity.<sup>92</sup> Finally yet importantly, possible intellectual impairment and lower life expectancy might influence the patient's decision to take anti-inflammatory and immunosuppressive drugs. Elderly patients will often choose a better quality of life and be less concerned about the risks of long-term side effects.

Cognitive deficit and depression is common among the elderly. After the age of 65, 17% of patients have a cognitive decline often rendering diagnosis and management of IBD more complicated.<sup>93</sup>

In addition, older patients may have more financial constraints and age-related functional capacity that limits management options.<sup>94</sup>

## Efficacy

There is no difference in the response rates with use of corticosteroids and aminosalicylates among the elderly and young age onset of IBD.<sup>95</sup> Similarly, no differences in efficacy have been noted with the use of thiopurines.<sup>96</sup> However, the benefit in terms of quality-adjusted life years has been questioned when starting azathioprine after age 65 in a study based on Markov modelling.<sup>85</sup>

The remission rates in both UC and CD were reported to be similar in young and elderly patients receiving anti-TNF therapy in an early retrospective study,<sup>47</sup> reflecting experience from data taken from the rheumatology literature.<sup>97</sup> However, later studies suggest somewhat reduced response rates in CD patients starting anti-TNFs in older age even after adjusting for duration of disease, indicating that pharmacokinetic or other mechanisms may play a role in the lower treatment response.<sup>98–100</sup> In a recent nested case controlled study conducted in Leuven,<sup>100</sup> the efficacy and safety of anti-TNFs among patients >65 years was compared to those starting before age 65 [after Charlson co-morbidity index adjustment]. This study showed a lower rate of short-term clinical response at 10 weeks [68% vs 89%;  $p < 0.001$ ] but the differences were not significant at 6 months [79.5% vs 82.8%;  $p = 0.63$ ], possibly indicating that the time to treatment effect is prolonged in elderly patients. In another study by Desai *et al.*,<sup>99</sup> only 61% of patients older than 60 had a partial or complete response to anti-TNFs compared to 83% of young anti-TNF-treated patients. Furthermore, in their study, elderly patients had a higher probability of stopping anti-TNFs, due mainly to adverse events. Mayo clinic data also suggest a lower rate of response at 6 months in older patients treated with anti-TNFs.<sup>98</sup>

The data from the rheumatology and dermatology literature suggest no differences in efficacy of methotrexate in older patients.<sup>101,102</sup> Methotrexate has not been studied in an exclusive cohort of IBD patients but retrospective cohort data indicate limited use in the elderly with similar outcomes compared to young patients.<sup>103</sup>

## ECCO Current Practice Position 8

There is no evidence that the efficacy of medical treatment in elderly IBD patients differs from that in younger adult patients

## Mono vs combination therapy in elderly patients

Several studies have suggested a higher efficacy of combination therapy with immunosuppressants and anti-TNF antibodies compared to monotherapy, especially regarding steroid-free remission.<sup>104–106</sup> However, no such study has been performed in the elderly and the number of older patients included in the aforementioned studies was negligible. Therefore, effectiveness of combination therapy in the elderly can only be extrapolated.

Immunosuppressive medications, especially when used in combination with other medications, and older age are associated with an increased risk for opportunistic infections including TB.<sup>45,98,107</sup> Moreover, combination immunosuppression in older patients was associated with a twofold increase in cessation of therapy.<sup>99</sup> Regarding mortality, a study from the Mayo Clinic showed that three out of four deaths attributable to infliximab treatment were in patients aged >65 years. Notably, these patients had a longer disease course [15–26 years], severe disease and comorbid conditions, and they were on concomitant immunomodulator therapy.<sup>98</sup> In contrast, some other studies showed no further increase in the odds of developing [serious] infections with combination therapy compared to monotherapy.<sup>47,108</sup>

The use of anti-TNF agents with immunomodulators is associated with an increased risk of developing non-Hodgkin lymphoma in adult CD patients.<sup>82,109</sup> Two additional studies found a predominance of lymphoma among older persons and among men.<sup>110,111</sup> The study from the French CESAME group identified older age, male sex and longer duration of IBD as the main risk factors for developing a lymphoproliferative disorder.<sup>81</sup> Regarding age, the hazard ratio per 1-year increase was 1.06. Of the 23 patients who were diagnosed with incident lymphoproliferative disorders, 12 were >60 years. In a multivariate analysis, the hazard ratio for malignant lymphoma of patients who received thiopurines was 5.3. This risk was further elevated for patients receiving a combination therapy [SIR = 6.5].<sup>81</sup> In younger patients the absolute risk is low, but in the elderly population the risk is considered clinically meaningful [1 in 300–400 in those over 70].<sup>81,112</sup>

## Safety

There is a potential for increased risk of nephrotoxicity in older patients using aminosalicylates and sulfasalazine due to slower elimination of these drugs and, particularly in those patients with comorbidities such as heart failure and pre-existing renal dysfunction, careful monitoring is warranted.<sup>113,114</sup>

All the available data indicate an even higher risk for serious adverse events with prolonged use of corticosteroids in elderly patients with IBD when compared to younger patients on long-term steroid therapy. In a large study of elderly-onset IBD patients exposed to steroids, there was increased risk of infections compared with non-exposed patients [relative risk 2.3, 95% confidence interval 1.8–2.9], and patients with

recent exposure were more vulnerable.<sup>37</sup> In the TREAT registry<sup>35</sup> age along with use of corticosteroids and narcotics were independent predictors of mortality. Other specific problems relate to osteoporosis-related fractures, osteonecrosis, alteration in mental status, fluid retention, ocular problems and drug interactions.<sup>115</sup>

#### **ECCO Current Practice Position 9**

All available data indicate a higher risk of serious adverse events with prolonged use of corticosteroids in elderly patients with IBD when compared to younger adult patients

In general, thiopurines are well tolerated and have a relatively low incidence of adverse events in elderly IBD patients.<sup>96</sup> However, there are consistent data indicating that the use of thiopurines in IBD increases not only the risk of infection but also the risk of lymphoproliferative disorders and skin cancers in elderly IBD patients.<sup>80,82,116</sup> More specifically, the CESAME study<sup>81</sup> showed that older age is an independent risk factor for the development of lymphomas, with more than 50% of the incident cases diagnosed in patients >60 years and with the risk increasing annually with ongoing, but not prior to, therapy with thiopurines.

#### **ECCO Current Practice Position 10**

The use of thiopurines in the elderly needs careful consideration and monitoring due to potential drug interactions, increased risk of lymphoma, non-melanoma skin cancer and infection

Old age is an independent risk factor for adverse events in IBD patients regardless of their medication use. In a cohort study of 734 IBD patients treated with anti-TNF, in comparison with 666 IBD patients on other medical treatments, the only independent risk factor for death was age at first anti-TNF use.<sup>117</sup> Mayo clinic data also suggested a significant increase in risk of infections in older patients with a twofold risk in discontinuation of therapy as a result of infections.<sup>98</sup> Similar data were reported by Desai *et al.*,<sup>99</sup> who observed a threefold risk of discontinuation of anti-TNF users who started therapy beyond the age of 60 compared to older azathioprine users. In a multicentre observational study, Cottone *et al.*<sup>47</sup> reported that elderly patients treated with biologic therapy (infliximab [ $n = 2475$ ] or adalimumab [ $n = 604$ ]) had an increased risk of infections, malignancy and mortality when compared to a younger group [13% vs 2.6%, 3% vs 0% and 10% vs 1%, respectively] or to elderly patients treated with other drugs. Similar results were observed in a more recent study conducted in Leuven, which also reported that the risk of severe adverse events was higher in patients over 65 on anti-TNF [relative risk = 4.7;  $p < 0.001$ ] with both malignancy and infections being higher in this group.<sup>100</sup> Furthermore, in that study, some of the deaths were due to cardiovascular complications, possibly suggesting the need for cardiovascular screening in elderly patients before starting anti-TNF therapy. Aggravation of heart failure with excess mortality following anti-TNF use in the elderly has also been reported previously in rheumatology patients.<sup>118</sup>

#### **ECCO Current Practice Position 11**

Elderly IBD patients treated with TNF inhibitors for IBD have an increased risk of severe infection compared with younger patients

While there are no data on the safety profile of methotrexate specific to elderly IBD patients, caution should be exercised in this group as the gastrointestinal and myelotoxicity from methotrexate is observed more frequently in elderly patients receiving methotrexate for rheumatoid arthritis.<sup>101,102</sup> Furthermore, renal toxicity will be increased by use of methotrexate in conjunction with NSAIDs due to decreased renal excretion.<sup>119</sup> Cyclosporine use in elderly IBD patients is best avoided and, if used, needs to be closely monitored given the risk profile related to co-morbidities such as hypertension and renal disease in these patients.<sup>120</sup>

#### **Drug interactions**

Due to polypharmacy, the potential for drug interactions is higher in elderly IBD patients. Accelerated corticosteroid clearance potentially resulting in reduced efficacy in IBD has been noted with the use of anti-epileptics.<sup>121</sup> Corticosteroids also may alter the action of anticoagulants.<sup>122</sup> Interaction with warfarin producing reduced anticoagulant activity has been recorded also with azathioprine.<sup>123</sup> In contrast, 5-aminosalicylates increase the anticoagulant activity of warfarin.<sup>124</sup> One of the well-described interactions of thiopurines is the xanthine oxidase-mediated action of allopurinol, which substantially increases the risk of myelotoxicity<sup>125</sup> and this is particularly relevant in elderly patients due to increased use of allopurinol in this cohort, but the interaction has also been used more recently to augment the therapeutic effect and reduce hepatotoxicity in IBD patients with a 75% reduction in the thiopurine dose.<sup>126</sup>

#### **ECCO Current Practice Position 12**

Polypharmacy from existing co-morbidities may be more common in elderly IBD patients and the potential for drug interactions must be considered

Problems with administration [e.g. rectal therapies] merit careful consideration

#### **Thrombotic complications, anticoagulation and antiplatelet therapy**

Antithrombotic prophylaxis should be considered in all hospitalized elderly patients with IBD. Treatment of venous thromboembolism in IBD should follow established antithrombotic therapy options taking into account a potentially increased risk of bleeding.<sup>127</sup>

Non-pharmacological prophylaxis includes hydration, correction of vitamin deficiencies [particularly vitamins B6 and B12 and folate] that can reduce homocysteine levels, graduated compression stockings or pneumatic devices, and early mobilization after surgery should be always considered, especially in hospitalized elderly IBD patients.<sup>128–131</sup> The Lenox Hill Hospital experience with 41 IBD patients on aspirin and clopidogrel for coronary artery disease also showed no change in the frequency of IBD flares in most patients on antiplatelet therapy when compared to a control group not on such therapy.<sup>132</sup> Indeed, an 11% reduction in IBD flares was noted in patients on antiplatelet therapy.<sup>132</sup> In another study of aspirin use in elderly CD patients with vascular disease no difference in hospitalization was noted in patients taking aspirin and those not on aspirin.<sup>88</sup>

An important issue to be considered particularly in active IBD patients is the potential risk of bleeding requiring careful dose finding studies and close clinical monitoring. Despite concerns that even low-dose aspirin may exacerbate IBD, such data and the lack of

credible data arguing against its use, it seems prudent to offer aspirin to patients with associated cardiovascular co-morbidity where compelling evidence exists to support its use.<sup>133,134</sup>

### ECCO Current Practice Position 13

In general, IBD patients are at increased risk for thrombotic complications which represent an important cause of morbidity and mortality. There is no evidence that the intensity or frequency of an IBD flare is increased by antiplatelet therapy. It is prudent to offer aspirin to patients with associated cardiovascular comorbidity where compelling evidence exists to support its use

### Withdrawal

No withdrawal trials of immunosuppressive agents or anti-TNF therapy have been performed specifically in the elderly. Earlier studies suggested that older age is associated with a lower risk of recurrence in patients who were either maintained on azathioprine/6-mercaptopurine or withdrew the drug.<sup>135–137</sup> In contrast, more recent studies did not confirm these findings: older age was not found to be predictive of relapse in either univariate or multivariate analysis in either disease.<sup>138–142</sup> Moreover, age was not associated with colectomy after drug withdrawal.<sup>138</sup> In CD patients on combination therapy [infliximab and azathioprine] in which azathioprine was discontinued, age was not a predictor of infliximab failure after azathioprine cessation.<sup>143</sup> Notably, most of these recent studies have been performed after a longer treatment duration as compared to the earlier trials.

## Surgical treatment

### Necessity of surgery for IBD

In elderly IBD patients, four studies reported low rates of total colectomy [0–2.1%] and segmental colectomy [0–4%].<sup>34,144–146</sup> Elderly UC patients were less likely to undergo surgery compared to younger UC patients [5.9 vs 18.2%,  $p = 0.03$ ]<sup>146</sup> with an odds ratio of 0.70 in another study.<sup>147</sup> Late-onset UC patients [>50 years] experienced no significant difference in requiring colectomy at 1 year of diagnosis compared to early-onset UC patients [18–30 years old]<sup>145</sup> In severe UC, early surgery has been recommended for elderly patients in order to reduce complications.<sup>148</sup>

In CD patients, the necessity for surgery appears to be lower with a higher age at the onset of disease.<sup>149</sup> If surgery for CD complications is necessary, the technical approach is not different from that used in younger patients: evacuation of abscesses, resection of stenoses or strictureplasty as a bowel-sparing intervention.<sup>31,122</sup>

### Complications

Although several risk factors for postoperative morbidity and mortality increase with age, increasing age itself remains an important risk factor for postoperative morbidity and mortality. A retrospective study of elderly UC patients showed no statistically significant difference in surgical morbidity or 30-day mortality between patients who underwent proctocolectomy with ileostomy and those who underwent ileoanal anastomosis or restorative proctocolectomy alone.<sup>144,150</sup> Additionally, no difference was found in surgical morbidity or 30-day mortality between the proctocolectomy with ileal pouch–anal anastomosis and those with ileostomy regardless of age.<sup>144,151</sup> The incidence of anastomotic leaks, pouch-related septic complications<sup>152</sup> and pouch failure rates did not differ between younger and older patients undergoing surgery for UC in Cleveland

Clinic, a high-volume pouch centre.<sup>153–155</sup> However, in other reports, an increased frequency of long-term complications such as pouchitis, anastomotic stricture or deterioration in pouch function in elderly patients undergoing ileal pouch–anal anastomosis has been reported.<sup>156,157</sup>

### Functional outcome after surgery

Functional outcome after ileal anal pouch surgery has been encouraging in the elderly, if the patient had a good anal sphincter function preoperatively.<sup>150,153,155,156,158</sup> The double-stapled technique has resulted in a much better functional outcome compared to hand-sewn anastomosis in patients over 50 or 55 years.<sup>150,155,158,159</sup> with a low risk of malignancy [<1% after 10 years] in the remaining rectal mucosal cuff patients.<sup>160–162</sup> Due to a higher chance of impaired sphincter function, total colectomy with permanent ileostomy may be offered to these elderly patients.<sup>90,122,163,164</sup> One study indicated that older veterans were less likely to have problems such as leakage or adjusting to the ileostomy than younger veterans.<sup>165</sup> In contrast, another study suggested that older patients were more likely to have difficulty with the daily management of their stoma, although their overall quality of life was equal to or better than that of younger patients who had undergone ileostomy.<sup>166</sup> Notably, in individual patients, ileorectal anastomosis may be considered, as well.<sup>122</sup>

### Postoperative recurrence in CD

Disparate reports in the literature have noted recurrence rates in the elderly after CD surgery ranging from five times greater than to equal to the recurrence rates in younger patients.<sup>152,167,168</sup> In one study, recurrence after bowel resection in elderly CD patients was reported to be less common than in younger patients [43 vs 64%], but when it occurred, the time to recurrence was significantly shorter in elderly patients [3.7 vs 5.8 years].<sup>169</sup> This improved prognosis may in part derive from the fact that the elderly have less small bowel and penetrating disease than younger patients, a profile that has been associated with decreased risk of disease recurrence.<sup>170,171</sup> No trials regarding prophylaxis of postoperative recurrence were performed specifically in the elderly.

### ECCO Current Practice Position 14

The indications for surgery are not different between elderly and younger adult patients in both CD and UC, and age alone is not an accurate predictor of surgical risk in IBD patients. In UC, the surgical approach of patients requiring pouch surgery is not different from younger adult patients. However, due to a possibly decreased anal sphincter function, the option of pouch versus ileostomy should be discussed in elderly patients

## Working groups

WG1: The elderly IBD patient: Difference in clinical course and diagnosis and the incidence and relevance of comorbidities and co-medication.

Leader—Paolo Gionchetti, Italy

Member—Christian Maaser, Germany

Member—Michael Mendall, UK

Member—Dimitrios Karagiannis, Greece

Y-ECCO—Pantelis Karatzas, Greece

N-ECCO—Nienke Ipenburg, The Netherlands

WG2: The elderly IBD patient: Differences in medical treatment, side effects of medical interventions and surgical management.

Leader—Andreas Sturm, Germany

Member—Shaji Sebastian, UK

Member—Fernando Rizzello, Italy

Member—Jimmy K. Limdi, UK

Member—Konstantinos Katsanos, Greece

Member—Carsten Schmidt, Germany

Y-ECCO—Steven Jeuring, The Netherlands

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Glen Doherty, Ireland; Stephan R. Vavricka, Switzerland.

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This manuscript is a joint expert consensus activity. Hence all authors participated sufficiently, intellectually or practically, in the work to take public responsibility for the content of the article, including the conception, design, data interpretation and writing of the manuscript. The final version of the manuscript was approved by all authors.

## References

- Jeuring SF, van den Heuvel TR, Zeegers MP, et al. Epidemiology and long-term outcome of inflammatory bowel disease diagnosed at elderly age – an increasing distinct entity? *Inflamm Bowel Dis* 2016;22:1425–34.
- Nguyen GC, Sheng L, Benchimol EI. Health care utilization in elderly onset inflammatory bowel disease: A population-based study. *Inflamm Bowel Dis* 2015;21:777–82.
- Taleban S, Colombel JF, Mohler MJ, Fain MJ. Inflammatory bowel disease and the elderly: A review. *J Crohns Colitis* 2015;9:507–15.
- Ananthakrishnan AN, Shi HY, Tang W, et al. Systematic review and meta-analysis: Phenotype and clinical outcomes of older-onset inflammatory bowel disease. *J Crohn's Colitis* 2016;10:1224–36.
- Erusalimsky JD, Grillari J, Grune T, et al. In search of 'omics'-based biomarkers to predict risk of frailty and its consequences in older individuals: The frailomic initiative. *Gerontology* 2016;62:182–90.
- Molodecky NA, Soon IS, Rabi DM, et al. Increasing incidence and prevalence of the inflammatory bowel diseases with time, based on systematic review. *Gastroenterology* 2012;142:46–54.
- Ng SC, Tang W, Ching JY, et al. Incidence and phenotype of inflammatory bowel disease based on results from the asia-pacific crohn's and colitis epidemiology study. *Gastroenterology* 2013;145:158–65.
- Bernstein CN, Wajda A, Svenson LW, et al. The epidemiology of inflammatory bowel disease in Canada: A population-based study. *Am J Gastroenterol* 2006;101:1559–68.
- Norgard BM, Nielsen J, Fonager K, et al. The incidence of ulcerative colitis (1995–2011) and crohn's disease (1995–2012)—based on nationwide Danish registry data. *J Crohns Colitis* 2014;8:1274–80.
- Herrinton LJ, Liu L, Lewis JD, Griffin PM, Allison J. Incidence and prevalence of inflammatory bowel disease in a Northern California managed care organization, 1996–2002. *Am J Gastroenterol* 2008;103:1998–2006.
- Gearry RB, Richardson A, Frampton CM, et al. High incidence of Crohn's disease in Canterbury, New Zealand: Results of an epidemiologic study. *Inflamm Bowel Dis* 2006;12:936–43.
- Nerich V, Monnet E, Etienne A, et al. Geographical variations of inflammatory bowel disease in France: A study based on national health insurance data. *Inflamm Bowel Dis* 2006;12:218–26.
- Romberg-Camps MJ, Hesselink-van de Kruijs MA, Schouten LJ, et al. Inflammatory bowel disease in south Limburg (the Netherlands) 1991–2002: Incidence, diagnostic delay, and seasonal variations in onset of symptoms. *J Crohns Colitis* 2009;3:115–24.
- Ronnblom A, Samuelsson SM, Ekblom A. Ulcerative colitis in the county of Uppsala 1945–2007: Incidence and clinical characteristics. *J Crohns Colitis* 2010;4:532–6.
- Lakatos PL, David G, Pandur T, et al. IBD in the elderly population: Results from a population-based study in western Hungary, 1977–2008. *J Crohns Colitis* 2011;5:5–13.
- Loftus EV Jr, Silverstein MD, Sandborn WJ, et al. Ulcerative colitis in Olmsted county, Minnesota, 1940–1993: Incidence, prevalence, and survival. *Gut* 2000;46:336–43.
- Loftus EV Jr, Silverstein MD, Sandborn WJ, et al. Crohn's disease in Olmsted county, Minnesota, 1940–1993: Incidence, prevalence, and survival. *Gastroenterology* 1998;114:1161–8.
- Loftus CG, Loftus EV Jr, Harmsen WS, et al. Update on the incidence and prevalence of Crohn's disease and ulcerative colitis in Olmsted county, Minnesota, 1940–2000. *Inflamm Bowel Dis* 2007;13:254–61.
- Lapidus A. Crohn's disease in Stockholm county during 1990–2001: An epidemiological update. *World J Gastroenterol* 2006;12:75–81.
- Latour P, Louis E, Belaiche J. Incidence of inflammatory bowel disease in the area of liege: A 3 years prospective study (1993–1996). *Acta Gastroenterol Belg* 1998;61:410–3.
- Charpentier C, Salleron J, Savoye G, et al. Natural history of elderly-onset inflammatory bowel disease: A population-based cohort study. *Gut* 2014;63:423–32.
- Mendall MA, Gunasekera AV, John BJ, Kumar D. Is obesity a risk factor for Crohn's disease? *Dig Dis Sci* 2011;56:837–44.
- Khalili H, Ananthakrishnan AN, Konijeti GG, et al. Measures of obesity and risk of Crohn's disease and ulcerative colitis. *Inflamm Bowel Dis* 2015;21:361–8.
- Harpsoe MC, Basit S, Andersson M, et al. Body mass index and risk of autoimmune diseases: A study within the Danish National Birth Cohort. *Int J Epidemiol* 2014;43:843–55.
- Chan SS, Luben R, Olsen A, et al. Body mass index and the risk for crohn's disease and ulcerative colitis: Data from a European prospective cohort study (the IBD in EPIC study). *Am J Gastroenterol* 2013;108:575–82.
- Greenwald DA, Brandt LJ. Inflammatory bowel disease after age 60. *Curr Treat Options Gastroenterol* 2003;6:213–25.
- Triantafyllidis JK, Emmanouilidis A, Nicolakis D, et al. Crohn's disease in the elderly: Clinical features and long-term outcome of 19 Greek patients. *Dig Liver Dis* 2000;32:498–503.
- Harper PC, McAuliffe TL, Beeken WL. Crohn's disease in the elderly. A statistical comparison with younger patients matched for sex and duration of disease. *Arch Intern Med* 1986;146:753–5.
- Riegler G, Tartaglione MT, Carratu R, et al. Age-related clinical severity at diagnosis in 1705 patients with ulcerative colitis: A study by gisc (Italian colon-rectum study group). *Dig Dis Sci* 2000;45:462–5.
- Heresbach D, Alexandre JL, Bretagne JF, et al. Crohn's disease in the over-60 age group: A population based study. *Eur J Gastroenterol Hepatol* 2004;16:657–64.
- Polito JM, 2nd, Childs B, Mellits ED, et al. Crohn's disease: Influence of age at diagnosis on site and clinical type of disease. *Gastroenterology* 1996;111:580–6.
- Kalkan IH, Dagli U, Oztas E, Tunc B, Ulker A. Comparison of demographic and clinical characteristics of patients with early vs. adult vs. late onset ulcerative colitis. *Eur J Intern Med* 2013;24:273–7.
- Zimmerman J, Gavish D, Rachmilewitz D. Early and late onset ulcerative colitis: Distinct clinical features. *J Clin Gastroenterol* 1985;7:492–8.



34. Ananthakrishnan AN, McGinley EL, Binion DG. Inflammatory bowel disease in the elderly is associated with worse outcomes: A national study of hospitalizations. *Inflamm Bowel Dis* 2009;15:182–9.
35. Lichtenstein GR, Feagan BG, Cohen RD, *et al.* Serious infections and mortality in association with therapies for Crohn's disease: Treat registry. *Clin Gastroenterol Hepatol* 2006;4:621–30.
36. Gisbert JP, Chaparro M. Systematic review with meta-analysis: Inflammatory bowel disease in the elderly. *Aliment Pharmacol Ther* 2014;39:459–77.
37. Brassard P, Bitton A, Suissa A, *et al.* Oral corticosteroids and the risk of serious infections in patients with elderly-onset inflammatory bowel disease. *Am J Gastroenterol* 2014;109:1795–802.
38. Stuck AE, Minder CE, Frey FJ. Risk of infectious complications in patients taking glucocorticosteroids. *Rev Infect Dis* 1989;11:954–63.
39. Rahier JF, Magro F, Abreu C, *et al.* Second European evidence-based consensus on the prevention, diagnosis and management of opportunistic infections in inflammatory bowel disease. *J Crohns Colitis* 2014;8:443–68.
40. Schneeweiss S, Korzenik J, Solomon DH, *et al.* Infliximab and other immunomodulating drugs in patients with inflammatory bowel disease and the risk of serious bacterial infections. *Aliment Pharmacol Ther* 2009;30:253–64.
41. Kim HH, Kim YS, Han DS, *et al.* Clinical differences in *Clostridium difficile* infection based on age: A multicenter study. *Scand J Inf Dis* 2014;46:46–51.
42. Ananthakrishnan AN, McGinley EL. Infection-related hospitalizations are associated with increased mortality in patients with inflammatory bowel disease. *J Crohns Colitis* 2013;7:107–12.
43. Kariv R, Navaneethan U, Venkatesh PG, Lopez R, Shen B. Impact of *Clostridium difficile* infection in patients with ulcerative colitis. *J Crohns Colitis* 2011;5:34–40.
44. Nguyen GC, Kaplan GG, Harris ML, Brant SR. A national survey of the prevalence and impact of *Clostridium difficile* infection among hospitalized inflammatory bowel disease patients. *Am J Gastroenterol* 2008;103:1443–50.
45. Toruner M, Loftus EV Jr, Harmsen WS, *et al.* Risk factors for opportunistic infections in patients with inflammatory bowel disease. *Gastroenterology* 2008;134:929–36.
46. Naganuma M, Kunisaki R, Yoshimura N, Takeuchi Y, Watanabe M. A prospective analysis of the incidence of and risk factors for opportunistic infections in patients with inflammatory bowel disease. *J Gastroenterol* 2013;48:595–600.
47. Cottone M, Kohn A, Daperno M, *et al.* Advanced age is an independent risk factor for severe infections and mortality in patients given anti-tumor necrosis factor therapy for inflammatory bowel disease. *Clin Gastroenterol Hepatol* 2011;9:30–5.
48. Tsai SY, Yang TY, Lin CL, *et al.* Increased risk of varicella zoster virus infection in inflammatory bowel disease in an Asian population: A nationwide population-based cohort study. *Int J Clin Pract* 2015;69:228–34.
49. Kopylov U, Levin A, Mendelson E, *et al.* Prior Varicella Zoster virus exposure in IBD patients treated by anti-TNFs and other immunomodulators: Implications for serological testing and vaccination guidelines. *Aliment Pharmacol Ther* 2012;36:145–50.
50. Pilkinton MA, Talbot HK. Update on vaccination guidelines for older adults. *J Am Ger Soc* 2015;63:584–8.
51. Tomczyk S, Bennett NM, Stoecker C, *et al.* Use of 13-valent pneumococcal conjugate vaccine and 23-valent pneumococcal polysaccharide vaccine among adults aged  $\geq 65$  years: Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Morb Mortal Wkly Rep* 2014;63:822–5.
52. Dotan I, Werner L, Vigodman S, *et al.* Normal response to vaccines in inflammatory bowel disease patients treated with thiopurines. *Inflamm Bowel Dis* 2012;18:261–8.
53. Melmed GY, Agarwal N, Frenck RW, *et al.* Immunosuppression impairs response to pneumococcal polysaccharide vaccination in patients with inflammatory bowel disease. *Am J Gastroenterol* 2010;105:148–54.
54. Fiorino G, Peyrin-Biroulet L, Naccarato P, *et al.* Effects of immunosuppression on immune response to pneumococcal vaccine in inflammatory bowel disease: A prospective study. *Inflamm Bowel Dis* 2012;18:1042–7.
55. Hagihara Y, Ohfuji S, Watanabe K, *et al.* Infliximab and/or immunomodulators inhibit immune responses to trivalent influenza vaccination in adults with inflammatory bowel disease. *J Crohns Colitis* 2014;8:223–33.
56. Andrisani G, Frasca D, Romero M, *et al.* Immune response to influenza A/H1N1 vaccine in inflammatory bowel disease patients treated with anti-TNF- $\alpha$  agents: Effects of combined therapy with immunosuppressants. *J Crohns Colitis* 2013;7:301–7.
57. Cullen G, Bader C, Korzenik JR, Sands BE. Serological response to the 2009 H1N1 influenza vaccination in patients with inflammatory bowel disease. *Gut* 2012;61:385–91.
58. Van Assche G, Dignass A, Panes J, *et al.* The second European evidence-based consensus on the diagnosis and management of Crohn's disease: Definitions and diagnosis. *J Crohns Colitis* 2010;4:7–27.
59. Rutter M, Saunders B, Wilkinson K, *et al.* Severity of inflammation is a risk factor for colorectal neoplasia in ulcerative colitis. *Gastroenterology* 2004;126:451–9.
60. Peyrin-Biroulet L, Lepage C, Jooste V, *et al.* Colorectal cancer in inflammatory bowel disease: A population-based study (1976–2008). *Inflamm Bowel Dis* 2012;18:2247–51.
61. Lakatos L, Mester G, Erdelyi Z, *et al.* Risk factors for ulcerative colitis-associated colorectal cancer in a Hungarian cohort of patients with ulcerative colitis: Results of a population-based study. *Inflamm Bowel Dis* 2006;12:205–11.
62. Eaden JA, Abrams KR, Mayberry JF. The risk of colorectal cancer in ulcerative colitis: A meta-analysis. *Gut* 2001;48:526–35.
63. Gillen CD, Walmsley RS, Prior P, Andrews HA, Allan RN. Ulcerative colitis and Crohn's disease: A comparison of the colorectal cancer risk in extensive colitis. *Gut* 1994;35:1590–2.
64. Baars JE, Looman CW, Steyerberg EW, *et al.* The risk of inflammatory bowel disease-related colorectal carcinoma is limited: Results from a nationwide nested case-control study. *Am J Gastroenterol* 2011;106:319–28.
65. Beaugerie L, Svrcek M, Seksik P, *et al.* Risk of colorectal high-grade dysplasia and cancer in a prospective observational cohort of patients with inflammatory bowel disease. *Gastroenterology* 2013;145:166–75.
66. Nieminen U, Jussila A, Nordling S, Mustonen H, Farkkila MA. Inflammation and disease duration have a cumulative effect on the risk of dysplasia and carcinoma in IBD: A case-control observational study based on registry data. *Int J Cancer* 2014;134:189–96.
67. Jess T, Winther KV, Munkholm P, Langholz E, Binder V. Intestinal and extra-intestinal cancer in Crohn's disease: Follow-up of a population-based cohort in Copenhagen County, Denmark. *Aliment Pharmacol Ther* 2004;19:287–93.
68. Canavan C, Abrams KR, Mayberry J. Meta-analysis: Colorectal and small bowel cancer risk in patients with Crohn's disease. *Aliment Pharmacol Ther* 2006;23:1097–104.
69. Ekblom A, Helmick C, Zack M, Adami HO. Increased risk of large-bowel cancer in Crohn's disease with colonic involvement. *Lancet* 1990;336:357–9.
70. Winther KV, Jess T, Langholz E, Munkholm P, Binder V. Long-term risk of cancer in ulcerative colitis: A population-based cohort study from Copenhagen County. *Clin Gastroenterol Hepatol* 2004;2:1088–95.
71. Rutter MD, Saunders BP, Wilkinson KH, *et al.* Thirty-year analysis of a colonoscopic surveillance program for neoplasia in ulcerative colitis. *Gastroenterology* 2006;130:1030–8.
72. Manninen P, Karvonen AL, Huhtala H, *et al.* The risk of colorectal cancer in patients with inflammatory bowel disease in Finland: A follow-up of 20 years. *J Crohns Colitis* 2013;7:e51–7.
73. Lutgens MW, van Oijen MG, van der Heijden GJ, *et al.* Declining risk of colorectal cancer in inflammatory bowel disease: An updated meta-analysis of population-based cohort studies. *Inflamm Bowel Dis* 2013;19:789–99.
74. Brackmann S, Andersen SN, Aamodt G, *et al.* Relationship between clinical parameters and the colitis-colorectal cancer interval in a cohort of patients with colorectal cancer in inflammatory bowel disease. *Scand J Gastroenterol* 2009;44:46–55.
75. Baars JE, Kuipers EJ, van Haastert M, *et al.* Age at diagnosis of inflammatory bowel disease influences early development of colorectal cancer

- in inflammatory bowel disease patients: A nationwide, long-term survey. *J Gastroenterol* 2012;47:1308–22.
76. Tran AH, Man Ngor EW, Wu BU. Surveillance colonoscopy in elderly patients: A retrospective cohort study. *JAMA* 2014;174:1675–82.
  77. Beaugerie L. Use of immunosuppressants and biologicals in patients with previous cancer. *Dig Dis* 2013;31:254–9.
  78. Swoger JM, Regueiro M. Stopping, continuing, or restarting immunomodulators and biologics when an infection or malignancy develops. *Inflamm Bowel Dis* 2014;20:926–35.
  79. Beaugerie L, Carrat F, Colombel JF, et al. Risk of new or recurrent cancer under immunosuppressive therapy in patients with IBD and previous cancer. *Gut* 2014;63:1416–23.
  80. Kandiel A, Fraser AG, Korelitz BI, Brensinger C, Lewis JD. Increased risk of lymphoma among inflammatory bowel disease patients treated with azathioprine and 6-mercaptopurine. *Gut* 2005;54:1121–5.
  81. Beaugerie L, Brousse N, Bouvier AM, et al. Lymphoproliferative disorders in patients receiving thiopurines for inflammatory bowel disease: A prospective observational cohort study. *Lancet* 2009;374:1617–25.
  82. Siegel CA, Marden SM, Persing SM, Larson RJ, Sands BE. Risk of lymphoma associated with combination anti-tumor necrosis factor and immunomodulator therapy for the treatment of Crohn's disease: A meta-analysis. *Clin Gastroenterol Hepatol* 2009;7:874–81.
  83. Afif W, Sandborn WJ, Faubion WA, et al. Risk factors for lymphoma in patients with inflammatory bowel disease: A case-control study. *Inflamm Bowel Dis* 2013;19:1384–9.
  84. Kotlyar DS, Lewis JD, Beaugerie L, et al. Risk of lymphoma in patients with inflammatory bowel disease treated with azathioprine and 6-mercaptopurine: A meta-analysis. *Clin Gastroenterol Hepatol* 2015;13:847–58.
  85. Lewis JD, Schwartz JS, Lichtenstein GR. Azathioprine for maintenance of remission in Crohn's disease: Benefits outweigh the risk of lymphoma. *Gastroenterology* 2000;118:1018–24.
  86. Moran GW, Lim AW, Bailey JL, et al. Review article: Dermatological complications of immunosuppressive and anti-tnf therapy in inflammatory bowel disease. *Aliment Pharmacol Ther* 2013;38:1002–24.
  87. Benchimol EI, Cook SF, Erichsen R, et al. International variation in medication prescription rates among elderly patients with inflammatory bowel disease. *J Crohns Colitis* 2013;7:878–89.
  88. Juneja M, Baidoo L, Schwartz MB, et al. Geriatric inflammatory bowel disease: Phenotypic presentation, treatment patterns, nutritional status, outcomes, and comorbidity. *Dig Dis Sci* 2012;57:2408–15.
  89. Pardi DS, Loftus EV Jr, Camilleri M. Treatment of inflammatory bowel disease in the elderly: An update. *Drugs Aging* 2002;19:355–63.
  90. Ananthakrishnan AN, Binion DG. Treatment of ulcerative colitis in the elderly. *Dig Dis* 2009;27:327–34.
  91. Cross RK, Wilson KT, Binion DG. Polypharmacy and Crohn's disease. *Aliment Pharmacol Ther* 2005;21:1211–6.
  92. Buckley JP, Kappelman MD, Allen JK, Van Meter SA, Cook SF. The burden of comedication among patients with inflammatory bowel disease. *Inflamm Bowel Dis* 2013;19:2725–36.
  93. Graham JE, Rockwood K, Beattie BL, et al. Prevalence and severity of cognitive impairment with and without dementia in an elderly population. *Lancet* 1997;349:1793–6.
  94. Taleban S. Challenges in the diagnosis and management of inflammatory bowel disease in the elderly. *Curr Treat Options Gastroenterol* 2015;13:275–86.
  95. Gisbert JP, Marin AC, Chaparro M. Systematic review: Factors associated with relapse of inflammatory bowel disease after discontinuation of anti-tnf therapy. *Aliment Pharmacol Ther* 2015;42:391–405.
  96. Chaparro M, Ordas I, Cabre E, et al. Safety of thiopurine therapy in inflammatory bowel disease: Long-term follow-up study of 3931 patients. *Inflamm Bowel Dis* 2013;19:1404–10.
  97. Busquets N, Carmona L, Suris X. [Systematic review: Safety and efficacy of anti-TNF in elderly patients]. *Rheumatol Clin* 2011;7:104–12.
  98. Colombel JF, Loftus EV Jr, Tremaine WJ, et al. The safety profile of infliximab in patients with Crohn's disease: The Mayo Clinic experience in 500 patients. *Gastroenterology* 2004;126:19–31.
  99. Desai A, Zator ZA, de Silva P, et al. Older age is associated with higher rate of discontinuation of anti-TNF therapy in patients with inflammatory bowel disease. *Inflamm Bowel Dis* 2013;19:309–15.
  100. Lobaton T, Ferrante M, Rutgeerts P, et al. Efficacy and safety of anti-TNF therapy in elderly patients with inflammatory bowel disease. *Aliment Pharmacol Ther* 2015;42:441–51.
  101. Koller MD, Aletaha D, Funovits J, et al. Response of elderly patients with rheumatoid arthritis to methotrexate or TNF inhibitors compared with younger patients. *Rheumatology* 2009;48:1575–80.
  102. Piaserico S, Conti A, Lo Console F, et al. Efficacy and safety of systemic treatments for psoriasis in elderly patients. *Acta Derm Venereol* 2014;94:293–7.
  103. Gonzalez-Lama Y, Taxonera C, Lopez-Sanroman A, et al. Methotrexate in inflammatory bowel disease: A multicenter retrospective study focused on long-term efficacy and safety. The Madrid experience. *Eur J Gastroenterol Hepatol* 2012;24:1086–91.
  104. Colombel JF, Sandborn WJ, Reinisch W, et al. Infliximab, azathioprine, or combination therapy for Crohn's disease. *N Engl J Med* 2010;362:1383–95.
  105. Panaccione R, Ghosh S, Middleton S, et al. Combination therapy with infliximab and azathioprine is superior to monotherapy with either agent in ulcerative colitis. *Gastroenterology* 2014;146:392–400.
  106. Christophorou D, Funakoshi N, Duny Y, et al. Systematic review with meta-analysis: Infliximab and immunosuppressant therapy vs. infliximab alone for active ulcerative colitis. *Aliment Pharmacol Ther* 2015;41:603–12.
  107. Lorenzetti R, Zullo A, Ridola L, et al. Higher risk of tuberculosis reactivation when anti-TNF is combined with immunosuppressive agents: A systematic review of randomized controlled trials. *Ann Med* 2014;46:547–54.
  108. Deepak P, Stobaugh DJ, Ehrenpreis ED. Infectious complications of TNF-alpha inhibitor monotherapy versus combination therapy with immunomodulators in inflammatory bowel disease: Analysis of the Food and Drug Administration adverse event reporting system. *J Gastrointest Liver Dis* 2013;22:269–76.
  109. Herrinton LJ, Liu L, Weng X, et al. Role of thiopurine and anti-TNF therapy in lymphoma in inflammatory bowel disease. *Am J Gastroenterol* 2011;106:2146–53.
  110. Bernstein CN, Blanchard JF, Kliever E, Wajda A. Cancer risk in patients with inflammatory bowel disease: A population-based study. *Cancer* 2001;91:854–62.
  111. Lewis JD, Bilker WB, Brensinger C, et al. Inflammatory bowel disease is not associated with an increased risk of lymphoma. *Gastroenterology* 2001;121:1080–7.
  112. Subramaniam K, D'Rozario J, Pavli P. Lymphoma and other lymphoproliferative disorders in inflammatory bowel disease: A review. *J Gastroenterol Hepatol* 2013;28:24–30.
  113. Gisbert JP, Gonzalez-Lama Y, Mate J. 5-Aminosalicylates and renal function in inflammatory bowel disease: A systematic review. *Inflamm Bowel Dis* 2007;13:629–38.
  114. Muller AF, Stevens PE, McIntyre AS, Ellison H, Logan RF. Experience of 5-aminosalicylate nephrotoxicity in the United Kingdom. *Aliment Pharmacol Ther* 2005;21:1217–24.
  115. Akerkar GA, Peppercorn MA, Hamel MB, Parker RA. Corticosteroid-associated complications in elderly Crohn's disease patients. *Am J Gastroenterol* 1997;92:461–4.
  116. Long MD, Martin CF, Pipkin CA, et al. Risk of melanoma and non-melanoma skin cancer among patients with inflammatory bowel disease. *Gastroenterology* 2012;143:390–9.
  117. Fidler H, Schnitzler F, Ferrante M, et al. Long-term safety of infliximab for the treatment of inflammatory bowel disease: A single-centre cohort study. *Gut* 2009;58:501–8.
  118. Khanna D, McMahon M, Furst DE. Anti-tumor necrosis factor alpha therapy and heart failure: What have we learned and where do we go from here? *Arthritis Rheumatol* 2004;50:1040–50.
  119. Morgacheva O, Furst DE. Use of MTX in the elderly and in patients with compromised renal function. *Clin Exp Rheumatol* 2010;28:S85–94.
  120. Kornbluth A, Present DH, Lichtiger S, Hanauer S. Cyclosporin for severe ulcerative colitis: A user's guide. *Am J Gastroenterol* 1997;92:1424–8.
  121. Katz S, Pardi DS. Inflammatory bowel disease of the elderly: Frequently asked questions (FAQs). *Am J Gastroenterol* 2011;106:1889–97.
  122. Stallmach A, Hagel S, Gharbi A, et al. Medical and surgical therapy of inflammatory bowel disease in the elderly—prospects and complications. *J Crohns Colitis* 2011;5:177–88.

123. Vazquez SR, Rondina MT, Pendleton RC. Azathioprine-induced warfarin resistance. *Ann Pharmacother* 2008;42:1118–23.
124. Wells PS, Holbrook AM, Crowther NR, Hirsh J. Interactions of warfarin with drugs and food. *Ann Intern Med* 1994;121:676–83.
125. Vazquez-Mellado J, Morales EM, Pacheco-Tena C, Burgos-Vargas R. Relation between adverse events associated with allopurinol and renal function in patients with gout. *Ann Rheum Dis* 2001;60:981–3.
126. Curkovic I, Rentsch KM, Frei P, et al. Low allopurinol doses are sufficient to optimize azathioprine therapy in inflammatory bowel disease patients with inadequate thiopurine metabolite concentrations. *Eur J Clin Pharmacol* 2013;69:1521–31.
127. Papa A, Gerardi V, Marzo M, et al. Venous thromboembolism in patients with inflammatory bowel disease: Focus on prevention and treatment. *World J Gastroenterol* 2014;20:3173–9.
128. Dignass A, Lindsay JO, Sturm A, et al. Second European evidence-based consensus on the diagnosis and management of ulcerative colitis part 2: Current management. *J Crohns Colitis* 2012;6:991–1030.
129. Van Assche G, Dignass A, Bokemeyer B, et al. Second European evidence-based consensus on the diagnosis and management of ulcerative colitis part 3: Special situations. *J Crohns Colitis* 2013;7:1–33.
130. Mowat C, Cole A, Windsor A, et al. Guidelines for the management of inflammatory bowel disease in adults. *Gut* 2011;60:571–607.
131. Kornbluth A, Sachar DB. Ulcerative colitis practice guidelines in adults: American College of Gastroenterology, Practice Parameters Committee. *Am J Gastroenterol* 2010;105:501–23.
132. Vinod J, Vadada D, Korelitz BI, et al. The effect of antiplatelet therapy in patients with inflammatory bowel disease. *J Clin Gastroenterol* 2012;46:527–9.
133. Danese S, Motte C de L, Fiocchi C. Platelets in inflammatory bowel disease: Clinical, pathogenic, and therapeutic implications. *Am J Gastroenterol* 2004;99:938–45.
134. Tan VP, Chung A, Yan BP, Gibson PR. Venous and arterial disease in inflammatory bowel disease. *J Gastroenterol Hepatol* 2013;28:1095–113.
135. Bouhnik Y, Lemann M, Mary JY, et al. Long-term follow-up of patients with Crohn's disease treated with azathioprine or 6-mercaptopurine. *Lancet* 1996;347:215–9.
136. Hawthorne AB, Logan RF, Hawkey CJ, et al. Randomised controlled trial of azathioprine withdrawal in ulcerative colitis. *BMJ* 1992;305:20–2.
137. Kim PS, Zlatanic J, Korelitz BI, Gleim GW. Optimum duration of treatment with 6-mercaptopurine for Crohn's disease. *Am J Gastroenterol* 1999;94:3254–7.
138. Cassinotti A, Actis GC, Duca P, et al. Maintenance treatment with azathioprine in ulcerative colitis: Outcome and predictive factors after drug withdrawal. *Am J Gastroenterol* 2009;104:2760–7.
139. Lemann M, Mary JY, Colombel JF, et al. A randomized, double-blind, controlled withdrawal trial in Crohn's disease patients in long-term remission on azathioprine. *Gastroenterology* 2005;128:1812–8.
140. Wenzl HH, Primas C, Novacek G, et al. Withdrawal of long-term maintenance treatment with azathioprine tends to increase relapse risk in patients with Crohn's disease. *Dig Dis Sci* 2015;60:1414–23.
141. Fraser AG, Orchard TR, Jewell DP. The efficacy of azathioprine for the treatment of inflammatory bowel disease: A 30 year review. *Gut* 2002;50:485–9.
142. Kennedy NA, Kalla R, Warner B, et al. Thiopurine withdrawal during sustained clinical remission in inflammatory bowel disease: Relapse and recapture rates, with predictive factors in 237 patients. *Aliment Pharmacol Ther* 2014;40:1313–23.
143. Oussalah A, Chevaux JB, Fay R, et al. Predictors of infliximab failure after azathioprine withdrawal in Crohn's disease treated with combination therapy. *Am J Gastroenterol* 2010;105:1142–9.
144. Longo WE, Virgo KS, Bahadursingh AN, Johnson FE. Patterns of disease and surgical treatment among United States veterans more than 50 years of age with ulcerative colitis. *Am J Surg* 2003;186:514–8.
145. Ha CY, Newberry RD, Stone CD, Ciorba MA. Patients with late-adult-onset ulcerative colitis have better outcomes than those with early onset disease. *Clin Gastroenterol Hepatol* 2010;8:682–7.
146. Triantafyllidis JK, Emmanouilidis A, Pomonis E, et al. Ulcerative colitis in the elderly: Clinical patterns and outcome in 51 Greek patients. *J Gastroenterol* 2001;36:312–6.
147. Almog G, Sachar DB, Bodian CA, Greenstein AJ. Surgery for ulcerative colitis in elderly persons: Changes in indications for surgery and outcome over time. *Arch Surg* 2001;136:1396–400.
148. Navaneethan U, Parasa S, Venkatesh PG, Trikudanathan G, Shen B. Prevalence and risk factors for colonic perforation during colonoscopy in hospitalized inflammatory bowel disease patients. *J Crohns Colitis* 2011;5:189–95.
149. Tremaine WJ, Timmons LJ, Loftus EV Jr, et al. Age at onset of inflammatory bowel disease and the risk of surgery for non-neoplastic bowel disease. *Aliment Pharmacol Ther* 2007;25:1435–41.
150. Bauer JJ, Gorfine SR, Gelernt IM, Harris MT, Kreel I. Restorative proctocolectomy in patients older than fifty years. *Dis Colon Rectum* 1997;40:562–5.
151. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. *Ann Intern Med* 2009;151:264–9.
152. Katz S, Feldstein R. Inflammatory bowel disease of the elderly: A wake-up call. *Gastroenterol Hepatol (N Y)* 2008;4:337–47.
153. Delaney CP, Fazio VW, Remzi FH, et al. Prospective, age-related analysis of surgical results, functional outcome, and quality of life after ileal pouch-anal anastomosis. *Ann Surg* 2003;238:221–8.
154. Fazio VW, Tekkis PP, Remzi F, et al. Quantification of risk for pouch failure after ileal pouch anal anastomosis surgery. *Ann Surg* 2003;238:605–14; discussion 14–7.
155. Delaney CP, Dadvand B, Remzi FH, Church JM, Fazio VW. Functional outcome, quality of life, and complications after ileal pouch-anal anastomosis in selected septuagenarians. *Dis Colon Rectum* 2002;45:890–4.
156. Chapman JR, Larson DW, Wolff BG, et al. Ileal pouch-anal anastomosis: Does age at the time of surgery affect outcome? *Arch Surg* 2005;140:534–9.
157. Church JM. Functional outcome and quality of life in an elderly patient with an ileal pouch-anal anastomosis: A 10-year follow up. *Aust N Z J Surg* 2000;70:906–7.
158. Lewis WG, Sagar PM, Holdsworth PJ, Axon AT, Johnston D. Restorative proctocolectomy with end to end pouch-anal anastomosis in patients over the age of fifty. *Gut* 1993;34:948–52.
159. Dayton MT, Larsen KR. Should older patients undergo ileal pouch-anal anastomosis? *Am J Surg* 1996;172:444–7.
160. Thompson-Fawcett MW, Warren BF, Mortensen NJ. A new look at the anal transitional zone with reference to restorative proctocolectomy and the columnar cuff. *Br J Surg* 1998;85:1517–21.
161. Coull DB, Lee FD, Henderson AP, et al. Risk of dysplasia in the columnar cuff after stapled restorative proctocolectomy. *Br J Surg* 2003;90:72–5.
162. Zmora O, Spector D, Dotan I, et al. Is stapled ileal pouch anal anastomosis a safe option in ulcerative colitis patients with dysplasia or cancer? *Int J Colorectal Dis* 2009;24:1181–6.
163. Holubar SD, Privitera A, Cima RR, et al. Minimally invasive total proctocolectomy with Brooke ileostomy for ulcerative colitis. *Inflamm Bowel Dis* 2009;15:1337–42.
164. Vavricka SR, Rogler G. Treatment of severe ulcerative colitis: Differences in elderly patients? *Dig Dis* 2009;27:315–21.
165. Pittman J, Rawl SM, Schmidt CM, et al. Demographic and clinical factors related to ostomy complications and quality of life in veterans with an ostomy. *J Wound Ostomy Continence Nurs* 2008;35:493–503.
166. Stryker SJ, Pemberton JH, Zinsmeister AR. Long-term results of ileostomy in older patients. *Dis Colon Rectum* 1985;28:844–6.
167. Fleischer DE, Grimm IS, Friedman LS. Inflammatory bowel disease in older patients. *Med Clin North Am* 1994;78:1303–19.
168. Fabricius PJ, Gyde SN, Shouler P, et al. Crohn's disease in the elderly. *Gut* 1985;26:461–5.
169. Wagtmans MJ, Verspaget HW, Lamers CB, van Hogezaand RA. Crohn's disease in the elderly: A comparison with young adults. *J Clin Gastroenterol* 1998;27:129–33.
170. Aeberhard P, Berchtold W, Riedtmann HJ, Stadelmann G. Surgical recurrence of perforating and nonperforating Crohn's disease. A study of 101 surgically treated patients. *Dis Colon Rectum* 1996;39:80–7.
171. Sachar DB, Lemmer E, Ibrahim C, et al. Recurrence patterns after first resection for stricturing or penetrating Crohn's disease. *Inflamm Bowel Dis* 2009;15:1071–5.