



SPECIAL ARTICLE

# European evidence-based Consensus on the management of ulcerative colitis: Special situations

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## 8. Pouchitis

### 8.1. General

Proctocolectomy with ileal pouch-anal anastomosis (IPAA) is the procedure of choice for most patients with ulcerative colitis (UC) requiring colectomy.<sup>1</sup> Pouchitis is a non-specific inflammation of the ileal reservoir and the most common complication of IPAA in patients with UC.<sup>2-7</sup> Its frequency is related to the duration of the follow-up, occurring in up to 50% of patients 10 years after IPAA in large series from major referral centres.<sup>1-9</sup> The cumulative incidence of pouchitis in patients with an IPAA for familial adenomatous polyposis is much lower, ranging from 0 to 10%.<sup>10-12</sup> Reasons for the higher frequency of pouchitis in UC remain unknown. Whether the pouchitis more commonly develops within the first years after IPAA or whether the risk continues to increase with longer follow-up remains undefined.

#### ECCO Statement 8A

The diagnosis of pouchitis requires the presence of symptoms, together with characteristic endoscopic and histological abnormalities [EL3a, RGB]. Extensive colitis, extraintestinal manifestations (eg primary sclerosing cholangitis), being a non-smoker, p-ANCA positive serology, and non-steroidal anti-inflammatory drug use are possible risk factors for pouchitis [EL3b, RG D]

#### 8.1.1. Symptoms

After total proctocolectomy with IPAA, median stool frequency is 4 to 8 bowel movements<sup>1-4,13,14</sup> with 700 mL

of semiformed/liquid stool per day<sup>2,13,14</sup>. Symptoms related to pouchitis include increased stool frequency and liquidity, abdominal cramping, urgency, tenesmus and pelvic discomfort (2, 15). Rectal bleeding, fever, or extraintestinal manifestations may occur. Rectal bleeding is more often related to inflammation of the rectal cuff ("cuffitis"),<sup>16</sup> than to pouchitis. Poor faecal incontinence may occur in the absence of pouchitis after IPAA, but is more common in patients with pouchitis. Symptoms of pouch dysfunction in patients with IPAA may be caused by conditions other than pouchitis, including Crohn's disease of the pouch,<sup>17-19</sup> cuffitis,<sup>16</sup> and an irritable pouch.<sup>20</sup> This is why the diagnosis depends on endoscopy and biopsy in conjunction with symptoms.

#### 8.1.2. Endoscopy ('pouchoscopy')

Pouchoscopy and pouch mucosal biopsy should be performed in patients with symptoms compatible with pouchitis, in order to confirm the diagnosis.<sup>15</sup> Patients with an ileoanal pouch occasionally have a stricture at the pouch-anal anastomosis, so a gastroscope rather than a colonoscope may better be necessary for pouchoscopy. Endoscopic findings compatible with pouchitis include diffuse erythema caused by inflammation of the ileal pouch, which may be patchy, unlike that observed in UC. Characteristic endoscopic findings include oedema, granularity, friability, spontaneous or contact bleeding, loss of vascular pattern, mucous exudates, haemorrhage, erosions and ulceration.<sup>17</sup> Erosions and/or ulcers along the staple line do not necessarily indicate pouchitis. Characteristically, these findings are non-specific and lesions may be discontinuous, unlike the colorectal lesions in UC.<sup>18,21,22</sup> Biopsies should be taken from the pouch mucosa and from the afferent limb above the pouch, but not along the staple line.

### 8.1.3. Histopathology of pouchitis

Histological findings of pouchitis are also non-specific, including acute inflammation with polymorphonuclear leukocyte infiltration, crypt abscesses and ulceration, in association with a chronic inflammatory infiltrate.<sup>21,22</sup> There may be discrepancy between endoscopic and histologic findings in pouchitis, possibly related to sampling error.<sup>23,24</sup> Morphological changes of the epithelium lining the ileal pouch normally develop in the 12–18 months after ileostomy closure, characterised by flattening and a reduced number, or disappearance of the villi, leading to villous atrophy (“colonic metaplasia”).<sup>22–24</sup> Although the aetiology of pouchitis remains unknown, it can be inferred from the predilection for patients with UC and the response to antibiotic therapy that the bacterial flora and whatever predisposes to UC itself are involved in the pathogenesis of tissue damage in the ileoanal pouch.<sup>25,26</sup> Pouchitis tends to occur only after colonic metaplasia has developed in the pouch, although a causal association is unproven.

#### ECCO Statement 8B

The most frequent symptoms of pouchitis are increased number of liquid stools, urgency, abdominal cramping and pelvic discomfort. Fever and bleeding are rare [EL1c, RG B]. Routine pouchoscopy after clinical remission is not required [EL5, RG D]

### 8.1.4. Differential diagnosis

The clinical history and biopsies help discriminate between pouchitis, ischaemia, Crohn's disease (CD) and other rare forms of pouch dysfunction such as collagenous pouchitis, *Clostridium difficile* or cytomegalovirus pouchitis.<sup>27–29</sup> Secondary pouchitis, caused by pelvic sepsis, usually causes focal inflammation and should be considered. Biopsies taken from the ileum above the pouch may reveal pre-pouch ileitis as a cause of pouch dysfunction, although this usually causes visible ulceration that may be confused with Crohn's disease.<sup>30</sup> The possibility of non-specific ileitis caused by NSAIDs should be considered.<sup>31</sup>

### 8.1.5. Risk factors for pouchitis and pouch dysfunction

Reported risk factors for pouchitis include extensive UC,<sup>1,32</sup> backwash ileitis,<sup>32</sup> extraintestinal manifestations (especially primary sclerosing cholangitis),<sup>5,19,33</sup> being a *non-smoker*<sup>34</sup> and regular use of NSAIDs.<sup>31,35</sup> Interleukin-1 receptor antagonist gene polymorphisms<sup>36</sup> and the presence of perinuclear neutrophil cytoplasmic antibodies<sup>37</sup> are also associated with pouchitis. Not surprisingly studies are discordant with regard to the role of each risk factor. Some of the best data on risk factors come from the Cleveland Clinic.<sup>38</sup> 240 consecutive patients were classified as having healthy pouches ( $n=49$ ), pouchitis ( $n=61$ ), Crohn's disease ( $n=39$ ), cuffitis ( $n=41$ ), or irritable pouch syndrome ( $n=50$ ). The risk of developing pouchitis was increased 3–5 fold when the indication for IPAA was dysplasia (OR 3.89; 95% CI 1.69–8.98), or when the patient had never smoked (OR 5.09; 95% CI 1.01–25.69), or used NSAIDs (OR 3.24; 95% CI 1.71–6.13), or (perhaps surprisingly) had never used anxiolytics (OR 5.19; 95% CI 1.45–18.59). The risk of turning out to have Crohn's disease of the pouch was greatly increased by being a current smoker (OR 4.77; 95% CI,

1.39–16–25), and modestly associated by having a pouch of long duration (OR 1.20; 95% CI 1.12–1.30). Cuffitis was associated with symptoms of arthralgia (OR 4.13; 95% CI 1.91–8.94) and a younger age (OR 1.16; 95% CI 1.01–1.33). Irritable pouch syndrome is probably under-recognised, although is a common cause of pouch dysfunction when other causes (including a small volume pouch, incomplete evacuation and pouch volvulus) have been excluded and investigations are normal. The principal risk factor is the use of antidepressants (OR 4.17; 95% CI 1.95–8.92) or anxiolytics (OR 3.21; 95% CI 1.34–7.47), which suggests that these people may have had irritable bowel syndrome contributing to symptoms of colitis before pouch surgery.<sup>38</sup>

These risk factors should not preclude proctocolectomy if surgery is appropriate, but should inform pre-operative discussions with the patient and family. In particular the possibility that IBS may be contributing to symptoms of refractory UC should be considered and objective evidence of treatment refractory colitis obtained before surgery. If there is a disparity between preoperative and endoscopic appearance, or if the patient is on antidepressants, then the risk of pouch dysfunction after IPAA needs particularly careful consideration. Similarly, if a patient has primary sclerosing cholangitis, then it is appropriate to discuss the higher risk of pouchitis. This is appropriate management of expectations rather than a contraindication to appropriate surgery.

## 8.2. Pattern of pouchitis

### 8.2.1. Acute and chronic pouchitis

On the basis of symptoms and endoscopy, pouchitis can be divided into remission (normal pouch frequency) or active pouchitis (increased frequency with endoscopic appearances and histology consistent with pouchitis).<sup>15,39</sup> Active pouchitis may then be divided into acute or chronic, depending on the symptom duration. The threshold for chronicity is a symptom duration of >4 weeks. Up to 10% of patients develop chronic pouchitis requiring long-term treatment, and a small subgroup has pouchitis refractory to medical treatment.<sup>3</sup>

### 8.2.2. Scoring of pouchitis

The Pouchitis Disease Activity Index (PDAI) has been developed to standardize diagnostic criteria and assess the severity of pouchitis.<sup>15,39,40</sup> The PDAI is a composite score that evaluates symptoms, endoscopy and histology. Each component score has a maximum of 6 points. Patients with a total PDAI score  $\geq 7$  are classified as having pouchitis, so a patient has to have both symptoms and endoscopic or histological evidence of pouchitis and, ideally, all three. The problem is that about a quarter of patients with a high symptom score suggestive of pouchitis may not fulfil criteria for the diagnosis of pouchitis, as assessed by the PDAI, since endoscopic or histological criteria may be absent. Consequently a relatively large number of patients may be unnecessarily treated for pouchitis when symptoms are due to other conditions. Other scoring systems have been devised, including that by Moskowitz<sup>21</sup> and an index from Heidelberg. Comparisons with the PDAI<sup>41,42</sup> show that they are not interchangeable, but this affects clinical trials rather than clinical practice.

### 8.2.3. Recurrent pouchitis and complications

Pouchitis recurs in more than 50%.<sup>3,15,39</sup> Patients with recurrent pouchitis can broadly be grouped into three categories: infrequent episodes (<1/yr), a relapsing course (1–3 episodes/yr) or a continuous course. Pouchitis may further be termed treatment responsive or refractory, based on response to single-antibiotic therapy (see 8.3.2).<sup>7,9</sup> Although these distinctions are largely arbitrary, they help both patients and their physicians when considering management options to alter the pattern of pouchitis. Complications of pouchitis include abscesses, fistulae, stenosis of the pouch-anal anastomosis and adenocarcinoma of the pouch.<sup>7,27,39</sup> This latter complication is exceptional and almost only occurs when there is pre-existing dysplasia or carcinoma in the original colectomy specimen.

## 8.3. Medical treatment

### 8.3.1. Acute pouchitis: antibiotics

#### ECCO Statement 8C

The majority of patients respond to metronidazole or ciprofloxacin, although the optimum modality of treatment is not clearly defined [EL1b, RG B]. Side-effects are less frequent using ciprofloxacin [EL1c, RG B]. Antidiarrhoeal drugs may reduce the number of daily liquid stools in patients, independent of pouchitis [EL5, RGD]

Treatment of pouchitis is largely empirical and only small placebo-controlled trials have been conducted. Antibiotics are the mainstay of treatment, and metronidazole and ciprofloxacin are the most common initial approaches, often with a rapid response. The odds ratio of inducing a response using oral metronidazole compared with placebo in active chronic pouchitis was 26.67 (95% CI 2.31–308.01, NNT=2).<sup>43</sup> The randomised trials of both metronidazole and ciprofloxacin are, however, small.<sup>44–46</sup> The two have been compared in another small randomised trial.<sup>47</sup> Seven patients received ciprofloxacin 1 g/day and nine patients metronidazole 20 mg/kg/day for a period of 2 weeks. Ciprofloxacin lowered the PDAI score from 10.1±2.3 to 3.3±1.7 ( $p=0.0001$ ), whereas metronidazole reduced the PDAI score from 9.7±2.3 to 5.8±1.7 ( $p=0.0002$ ). There was a significantly greater reduction in the ciprofloxacin compared to metronidazole in terms of the total PDAI ( $p=0.002$ ), symptom score ( $p=0.03$ ) and endoscopic score ( $p=0.03$ ), as well as fewer adverse events (33% of metronidazole-treated patients reported side-effects, but none on ciprofloxacin). Combination antibiotic therapy is an option for persistent symptoms (below).

### 8.3.2. Chronic pouchitis: combination antibiotic therapy or budesonide

#### ECCO Statement 8D

In chronic pouchitis, combined antibiotic treatment is effective [EL1b, RG B]

For patients who have persistent symptoms, alternative diagnoses should be considered, including undiagnosed Crohn's disease, pouch-anal or ileal-pouch stricture, infec-

tion with CMV or *Cl difficile*, collagenous pouchitis, cuffitis, anatomical disorders, or irritable pouch syndrome. Approximately 10–15% of patients with acute pouchitis develop chronic pouchitis, which may be “treatment responsive” or “treatment refractory” to single-antibiotic therapy.<sup>39</sup> Patients with chronic, refractory pouchitis do not respond to conventional therapy and often continue to suffer symptoms, which is a common cause of pouch failure. Combination antibiotic therapy or oral budesonide may work. 16 consecutive patients with chronic, refractory pouchitis (disease >4 weeks and failure to respond to >4 weeks of single-antibiotic therapy) were treated with ciprofloxacin 1 g/day and tinidazole 15 mg/kg/day for 4 weeks.<sup>47</sup> A historic cohort of ten consecutive patients with chronic refractory pouchitis treated with 5–8 g oral and topical mesalazine daily was used as a comparator. These refractory patients had a significant reduction in the total PDAI score and a significant improvement in quality-of-life score ( $p<0.002$ ) when taking ciprofloxacin and tinidazole, compared to baseline. The rate of clinical remission in the antibiotic group was 87.5% and for the mesalazine group was 50%.

In another study, 18 patients non-responders to metronidazole, ciprofloxacin or amoxicillin/clavulanic acid for 4 weeks were treated orally with rifaximin 2 g/day (a nonabsorbable, broad spectrum antibiotic) and ciprofloxacin 1 g/day for 15 days. Sixteen out of 18 patients (88.8%) either improved ( $n=10$ ) or went into remission ( $n=6$ ).<sup>48</sup> Median PDAI scores before and after therapy were 11 (range 9–17) and 4 (range 0–16), respectively ( $p<0.002$ ). A British group observed similar benefit in just 8 patients.<sup>49</sup> In another combination study, 44 patients with refractory pouchitis received metronidazole 800 mg–1 g/day and ciprofloxacin 1 g/day for 28 days.<sup>50</sup> 36 patients (82%) went into remission and median PDAI scores before and after therapy were 12 and 3 respectively ( $p<0.0001$ ). The alternative is oral budesonide CIR 9 mg daily for 8 weeks, which achieved remission in 15/20 (75%) patients not responding after 1 month of ciprofloxacin or metronidazole.<sup>51</sup> The message is simple enough, even if the trials are underpowered: if ciprofloxacin does not work, then try it in combination with an imidazole antibiotic or rifaximin, or try oral budesonide.

### 8.3.3. Acute and chronic refractory pouchitis: other agents

The variety of approaches illustrates the challenges of trying to find treatment that works for a new disorder. These are largely of historic interest. Budesonide enemas were as effective as metronidazole for acute pouchitis in a randomised controlled trial.<sup>52</sup> Ciclosporin enemas were successful for chronic pouchitis in a pilot study<sup>53</sup> and oral azathioprine may help if patients relapse become budesonide-dependent. Uncontrolled studies of short-chain fatty acid enemas<sup>54,55</sup> showed little value. Glutamine and butyrate suppositories have been compared for chronic pouchitis.<sup>56</sup> Of more recent interest, infliximab has been tried in patients with chronic, (very) refractory pouchitis not responding either to metronidazole or ciprofloxacin 1 g/day for 4 weeks or oral budesonide CIR 9 mg/day for 8 weeks. 10/12 (83.3%) such patients treated with infliximab 5 mg/kg at 0, 2 and 6 weeks went into remission.<sup>57</sup> The median PDAI score before therapy was 13 (range 8–18) and 2 (range 0–9) after infliximab ( $p<0.001$ ) and the IBDQ also significantly improved from 96

(range 74–184) to 196 (92–230) ( $p < 0.001$ ).<sup>57</sup> Infliximab has been used when the cause of pouch dysfunction is Crohn's disease, or fistulation.<sup>58</sup> Benefit has also been reported from alicaforsen enemas (an inhibitor of intercellular adhesion molecule (ICAM)-1) in an open-label trial.<sup>59</sup>

#### 8.3.4. Maintenance of remission: probiotics

##### ECCO Statement 8E

VSL#3 ( $18 \times 10^{11}$  of 8 bacterial strains for 9 or 12 months) has shown efficacy for maintaining antibiotic-induced remission [EL1b, RG B]. VSL#3 ( $9 \times 10^{11}$  bacteria) has also shown efficacy for preventing pouchitis [EL2b, RG C]

In chronic pouchitis, once remission has been obtained, treatment with the highly concentrated probiotic mixture VSL#3 is able to maintain remission. Two double-blind, placebo-controlled studies have shown the efficacy of VSL#3 (450 billion bacteria of 8 different strains/g) to maintain remission in patients with chronic pouchitis. In the first study, 40 patients who achieved clinical and endoscopic remission after one month of combined antibiotic treatment (rifaximin 2 g/day + ciprofloxacin 1 g/day), were randomised to receive either VSL#3, 6 g/day ( $18 \times 10^{11}$  bacteria/day), or placebo for 9 months.<sup>60</sup> All 20 patients who received placebo relapsed, while 17 of the 20 patients (85%) treated with VSL#3 remained in clinical and endoscopic remission at the end of the study. Interestingly, all 17 patients relapsed within four months after stopping VSL#3.<sup>60</sup> In the second study, 36 patients with chronic, refractory pouchitis who achieved remission (PDAI=0) after 1 month of combined antibiotic treatment (metronidazole + ciprofloxacin) received 6 g/once a day of VSL#3 or placebo for 1 year. Remission rates at one year were 85% in the VSL#3 group and 6% in the placebo group ( $p < 0.001$ ).<sup>61</sup>

#### 8.3.5. Prevention of pouchitis: probiotics

The same probiotic preparation (VSL#3) has been shown to prevent pouchitis within the first year after surgery, in a randomised, double-blind, placebo-controlled study. Forty consecutive patients undergoing IPAA for UC were randomised within a week after ileostomy closure, to VSL#3 3 g ( $9 \times 10^{11}$ ) per day or placebo for 12 months. Patients were assessed clinically, endoscopically and histologically at 1, 3, 6, 9 and 12 months. Patients treated with VSL#3 had a significantly lower incidence of acute pouchitis (10%) compared with those treated with placebo (40%) ( $p < 0.05$ ), and experienced a significant improvement of quality of life.<sup>62</sup> The mechanism by which therapy with probiotics works remains elusive, but has been investigated.<sup>63</sup> Mucosa-associated pouch microbiota before and after therapy with VSL#3 shows that patients who develop pouchitis while treated with placebo have low bacterial and high fungal diversity. Bacterial diversity was increased and fungal diversity was reduced in patients in remission maintained with VSL#3 ( $p = 0.001$ ). Real time PCR experiments demonstrated that VSL#3 increased the total number of bacterial cells ( $p = 0.002$ ) and modified the spectrum of bacteria towards anaerobic species. Taxa-specific clone libraries showed that the spectrum of *Lactobacillus* sp. and *Bifidobacter* sp. was altered on probiotic therapy. The diversity of the fungal flora was repressed. Restoration of the integrity of

a "protective" intestinal mucosa related microbiota could therefore be a potential mechanism of probiotic bacteria in inflammatory barrier diseases of the lower gastrointestinal tract.

#### 8.4. Cuffitis

##### ECCO Statement 8E

Rectal cuff inflammation (cuffitis) may induce symptoms similar to pouchitis or irritable pouch syndrome, although bleeding is more frequent [EL2a, RG B]. Topical 5-ASA has shown efficacy [EL4, RGD]

Cuffitis, especially after double-stapled IPAA (see Section 7, preceding paper same issue) can cause pouch dysfunction with symptoms that mimic pouchitis or irritable pouch syndrome (IPS). Unlike IPS (which may coexist) bleeding is a characteristic feature of cuffitis. Endoscopy by an informed endoscopist is diagnostic, but care has to be taken to examine the cuff of columnar epithelium between the dentate line and pouch-anal anastomosis (Section 7.2.3, preceding paper same issue).<sup>64</sup> In an open-label trial, 14 consecutive patients with cuffitis were treated with mesalamine suppositories 500 mg twice daily.<sup>16</sup> Mesalamine suppositories significantly reduced the total Cuffitis Activity Index (derived from the PDAI) from  $11.9 \pm 3.17$  to  $6.21 \pm 3.19$  ( $p < 0.001$ ). Symptom subscore (from  $3.24 \pm 1.28$  to  $1.79 \pm 1.31$ ), endoscopy subscore (from  $3.14 \pm 1.29$  to  $1.00 \pm 1.52$ ) and histology subscore ( $4.93 \pm 1.77$  to  $3.57 \pm 1.39$ ) were all significantly reduced. 92% of patients with bloody bowel movements and 70% with arthralgia (a characteristic clinical feature of cuffitis, Section 8.1.5) improved on therapy. No systemic or topical adverse effects were reported.

#### 9. Surveillance for colorectal cancer

##### 9.1. Risk of cancer

###### 9.1.1. Estimation of risk

##### ECCO Statement 9A

Patients with longstanding ulcerative colitis appear to have an increased risk of colorectal cancer (CRC) as compared to the general population [EL2]

Patients with long standing UC have a higher risk of developing colorectal carcinoma (CRC) than the average population. The magnitude of this risk, however, is still the subject of a debate. Indeed, while older reports included in two meta-analyses<sup>65,66</sup> confirmed a rapid increase of the risk after ten years of disease, the magnitude of the risk in recent population-based studies appears much smaller.<sup>67,68</sup> In fact, although Eaden and colleagues computed a cumulative CRC risk of 18% in UC patients after 30 years of disease, risks of only 7.5% and 2.1% respectively were observed in two studies published since 2004.<sup>67,68</sup> Furthermore, in the largest report of surveillance colonoscopy in at-risk population of patients with extensive UC to date (600 patients over a 30 year period), the cumulative incidence of CRC by colitis duration

was 2.5% at 20 years, 7.6% at 30 years, and 10.8% at 40 years.<sup>69</sup> In this study from St Mark's, only 30/600 patients (5%) developed CRC. The reasons for such an improvement in the risk of CRC are still unclear but may include improved control of mucosal inflammation, more extensive use of 5-ASA compounds, the implementation of surveillance programmes and timely colectomy.<sup>70</sup> Taken together these studies suggest that the CRC risk in UC patients should be kept under scrutiny. Nevertheless, the best evidence, as provided by concordant meta-analyses, indicates that the risk of CRC development is increased in UC [EL2]. The ECCO Consensus working party, through their answers to questionnaires, supported this evaluation of the data.

### 9.1.2. Risk factors for cancer development

#### ECCO Statement 9B

Risk is highest in patients with extensive colitis, intermediate in patients with left-sided colitis, and not increased in proctitis [EL2].

Several independent factors affect the magnitude of the risk of malignant transformation. The duration of disease and extent of mucosal inflammation are the most prominent. There is no uniform definition of the duration of disease, although onset of symptoms has generally been used in the studies that have identified this parameter as a risk factor. In a review of 19 practice and population-based studies, Eaden confirmed that the CRC risk appears to increase 8–10 years after the onset of UC related symptoms<sup>65</sup> and subsequently increases in later decades of the disease [EL2].

#### ECCO Statement 9C

Patients with early onset of disease (age <20 years at onset of disease) and patients with UC-associated primary sclerosing cholangitis (PSC) may have a particularly increased risk [EL2]. Persistent inflammation and family history of CRC may contribute to the risk of CRC in patients with UC [EL3]

The extent of mucosal inflammation (including backwash ileitis) has been correlated with the risk of CRC in several studies, as well as in a systematic review [EL2].<sup>66,67,71–75</sup> Other factors have also been associated with a high CRC risk in all or part of these studies. These include young age at onset of the disease (less than 20 years of age at the time of diagnosis)<sup>65</sup> and an association with primary sclerosing cholangitis (PSC) [EL2].<sup>76</sup> However, there was no difference in median age at onset of colitis for those with or without CRC in the 600-patient study from St Mark's ( $p=0.8$ , Mann–Whitney) years.<sup>69</sup> The persistence of mucosal inflammation<sup>72,73</sup> or a family history of CRC<sup>77</sup> may also contribute to an increased risk, but the association has been less consistent across the studies [EL3]. In a nested case-control study from two well-defined, population-based IBD cohorts (Copenhagen County, Denmark and Olmsted County, Minnesota) 43 cases of IBD-associated CRC were matched on six criteria to 1–3 controls ( $n=102$ ). Significant associations were found between PSC (OR 6.9, 95% CI 1.2–40.0), the percentage of time with clinically active disease (OR per 5% increase 1.2,

95% CI 1.0–1.4), and  $\geq 12$  months of continuous symptoms (OR 3.2 95% CI 1.2–8.6).<sup>78</sup> The presence of pseudopolyps, which can be considered a marker of severity of inflammation, have been associated with double the risk of CRC (OR 2.5; 95% CI: 1.4–4.6),<sup>73,79</sup> which is a useful practice point for clinicians.

## 9.2. Surveillance colonoscopy programmes

### 9.2.1. Screening and surveillance

Since dysplastic changes in colonic mucosa are associated with an increased risk of CRC in UC, surveillance colonoscopy programmes have been developed with the aim of reducing morbidity and mortality due to CRC, while avoiding unnecessary prophylactic colectomy. Surveillance for CRC in patients with UC amounts to more than just performing repeated colonoscopies, but includes reviewing patient symptoms, medication use and laboratory values as well as updating personal and familial medical history. At the onset of these programmes, an initial *screening* colonoscopy is performed, with the goal of reassessing disease extent and confirming the absence of dysplastic lesions. Thereafter *surveillance* colonoscopies are regularly performed at defined intervals (below).

### 9.2.2. Effectiveness

#### ECCO Statement 9D

Surveillance colonoscopy may permit earlier detection of CRC, with a corresponding improved prognosis [EL3, RG B]. Unequivocal evidence that surveillance colonoscopy prolongs survival in patients with UC is lacking [EL3, RG B]

The effectiveness of these programmes has been evaluated in some prospective studies, systematically reviewed by the Cochrane collaboration.<sup>66</sup> An American consensus conference, held under the auspices of the Crohn's and Colitis Foundation of America, also reviewed the usefulness of screening and surveillance colonoscopies in 2005.<sup>80</sup> The Cochrane collaboration used death related to CRC as the primary endpoint for the evaluation of surveillance programmes in UC, limiting their analysis to prospective randomised studies that included a control group. The authors were unable to demonstrate a benefit of surveillance programmes for preventing CRC-related death in UC by these strict parameters, but included only two studies in their final analysis.<sup>81,82</sup> An earlier meta-analysis included a third study yet to be published in full, but concluded that there was an improved 5-year survival in patients undergoing surveillance, compared to UC patients outside surveillance programmes.<sup>83</sup> Furthermore, in the largest and most meticulous screening programme reported to date, involving 600 patients, 2627 colonoscopies, 5932 patient-years of follow-up and a caecal intubation rate of 98.7%, with no significant complications, 16/30 cancers were interval cancers.<sup>69</sup>

Unequivocal evidence for the benefit of these programmes is therefore lacking and the apparent benefit could still be linked to lead-time bias. Patients in surveillance programmes may have an earlier diagnosis of CRC even if CRC is detected independently of surveillance colonoscopy. Diagnosis of CRC in patients outside such programmes may arise from later,

symptom-driven investigation [EL3]. These issues are best discussed with patients before entry into a surveillance programme.

The Consensus had divided opinions regarding the ability of surveillance colonoscopy programmes to improve survival in UC patients, in keeping with the contrasting results of the meta-analyses. Only one third of the voting experts considered that the procedure could achieve this goal, while two-thirds remained unconvinced or attributed any benefit to potential lead-time bias. Nevertheless, it should be noted that any benefit estimated in years of life saved may be much greater in UC patients than for general population screening. This is because UC-related CRC tends to occur earlier in life and with a higher frequency than in the general population. Mathematical models have evaluated that the duration of life saved per case screened ranges from 1.2 to 5 years in UC patients, compared to 1.2 to 4 months in general population screening,<sup>66,84</sup> depending on the parameters included in the calculation.

### 9.2.3. Initial screening colonoscopy

#### ECCO Statement 9E

Screening colonoscopy should be offered 8–10 years after the onset of UC symptoms to all patients to reassess disease extent [EL5, RG D]

As duration of disease is a major risk factor for the development of CRC in UC patients, it is rational to propose a screening colonoscopy when the risk starts to increase, i.e. after 8–10 years from the onset of disease [EL2]. This initial colonoscopy also aims to reassess the extent of disease, since this parameter also impacts on the risk of CRC. Nevertheless, the appropriateness of screening colonoscopy as a way of reassessing disease extent and potential risk has not been formally established. It has been proposed in reviews and a prior consensus report,<sup>80</sup> as well as being agreed during the present Consensus conference by the participating experts [EL5].

### 9.2.4. Surveillance schedules

#### ECCO Statement 9F

In extensive colitis, surveillance should start after screening colonoscopy and be performed every other year up to year 20 of disease, then annually [EL2, RG B]. Surveillance should start 15 years after onset of disease in left-sided or distal UC. Proctitis does not require further surveillance [EL2, RG B]

The surveillance schedule is also arbitrary, but because CRC has been observed within 2 years of surveillance colonoscopy,<sup>85,86</sup> intervals between repeat investigations should not exceed this and should be shorter in patients with particularly high risks such as those with longstanding disease or PSC.

Furthermore, although disease extent is central to CRC risk assessment, this parameter may be difficult to define, implying that surveillance may be offered to large groups of patients. Considerable differences between extent assessed by colonoscopy and histology have been reported,<sup>87</sup> as well

as variations in extent over time.<sup>88</sup> Neoplasia has been reported in areas of microscopic involvement without endoscopically visible inflammation. Thus, disease extent should be defined not only by the outcome of screening colonoscopy, but also by the results of previous procedures. In contrast, there is good evidence that the CRC risk is lower in patients with limited disease<sup>71,75</sup> as defined by colonoscopy or barium enema, so a reasonable compromise is to defer surveillance until later time points in patients with limited macroscopic disease [EL2]. This all assumes that a decision has been made with the patient that surveillance is appropriate. If the risk of CRC complicating colitis is thought to be no higher than the general population, surveillance may be considered unnecessary.

#### ECCO Statement 9G

If primary sclerosing cholangitis (PSC) is associated to UC, surveillance should be performed annually from the time of PSC diagnosis [EL3, RG B]

In other situations, such as patients with UC-associated PSC, the risk of developing a CRC is not only particularly high, but has been reported to occur early (median 2.9 years) in the course of the disease.<sup>89</sup> These patients should enter in a more intensive surveillance programme once the diagnosis of PSC has been established.

The recommendations by ECCO (Statements 9E–9G) are contingent on a perceived increased risk of CRC in UC (Statements 9A–9C) and widespread acceptance in several European countries that screening for CRC in the general population is appropriate. If the latter applies, it is difficult to justify failure to screen a group of patients with higher risk of CRC more closely. The recommendation grades are appropriate to the strength of the evidence.

## 9.3. Colonoscopic procedures

### 9.3.1. Number and site of biopsies

Evidence for procedural techniques during surveillance colonoscopy is better documented than the benefit of the programme itself. At least 33 biopsies should be obtained from the various segments of the colon to achieve 90–95% sensitivity for the detection of dysplasia.<sup>90–93</sup> A reasonable approach would therefore to perform 4 random biopsies every 10 cm around the colon. Extra biopsies should be obtained from strictured or raised areas and from other abnormal areas in the colon. Full colonoscopy is necessary because about a third of UC-associated CRC develop in the proximal colon.<sup>85</sup> This strategy is further supported by the observation that most dysplastic lesions are visible during careful colonoscopy. In a study performed on 525 patients who underwent 2204 surveillance colonoscopies, Rutter detected 110 neoplastic areas in 56 patients.<sup>94</sup> Eighty-five (77.3%) were macroscopically visible at colonoscopy and 25 (22.7%) were macroscopically invisible. Fifty patients (89.3%) had macroscopically detectable neoplasia, while only 6 (10.7%) had macroscopically invisible lesions. The value of random biopsies, however, is limited compared to optical techniques that enhance detection of dysplastic epithelium.



### 9.3.2. Chromoendoscopy

#### ECCO Statement 9H

Random biopsies (4 every 10 cm) and targeted biopsies of any visible lesion should be performed during surveillance colonoscopy [EL2b, RG B]. Methylene blue or indigo carmine chromoendoscopy is an alternative to random biopsies for appropriately trained endoscopists and is superior to random biopsies in the detection rate of neoplastic lesions [EL1b, RG B]

The yield of surveillance colonoscopy can be improved by spraying dyes (such as methylene blue or indigo carmine) that highlight subtle changes in the architecture of the colonic mucosa.<sup>95–101</sup> All studies have confirmed an improved diagnostic yield for dysplasia detection using chromoendoscopy. With this method, random biopsies of apparently normal mucosa is of no additional value compared to targeted biopsies obtained after dye staining of the mucosa.<sup>101</sup> Comparable diagnostic yields from chromoendoscopy have been obtained with both methylene blue and indigo carmine.<sup>97,98</sup> Despite these good results, a single from experienced investigators found that no dysplasia was missed even without dye spraying.<sup>94</sup> However, trained endoscopists in chromoendoscopy may even further distinguish neoplastic from non-neoplastic changes, based on surface crypt architecture based on pit pattern recognition with a sensitivity of 93% and 97%, respectively. Colonoscopy with dye staining did not take significantly longer than conventional colonoscopy.<sup>98</sup> This endoscopic approach may not only improve the yield of screening and surveillance colonoscopies, but also decrease the workload of pathologists because fewer biopsies are needed per procedure.

## 9.4. Dysplasia

The ultimate goal of surveillance colonoscopy is to identify whether the colonic mucosa has already undergone the early steps of malignant transformation (i.e. to detect dysplasia), which identifies UC patients at the highest risk of CRC development.<sup>102,103</sup> Dysplasia in UC is stratified as low grade, high grade or indefinite for dysplasia, according to the presence or absence of specific histological changes in the epithelium. If biopsies are indefinite for dysplasia and this is confirmed by an experienced pathologist, then follow-up surveillance colonoscopy within 3 to 6 months is recommended, with intensification of UC therapy in the meantime.

### 9.4.1. Risk of progression to cancer

#### ECCO Statement 9I

A finding of dysplasia should be confirmed by an independent pathologist [EL2b, RG B]

The grade of dysplasia is important because it impacts on the sensitivity and specificity of the presence or future development of CRC. Dysplasia of any grade has been reported to have a 74% sensitivity and 74% sensitivity for CRC development, while in the same series from the Mayo

Clinic, high grade dysplasia had lower sensitivity (34%) but 98% specificity for CRC detection.<sup>104</sup> In the most recent meta-analysis, low-grade dysplasia was found to be associated with a 9-fold increased risk of developing CRC and a 12-fold risk of developing advanced neoplasia.<sup>105</sup> Therefore, the finding of low-grade dysplasia carries a substantial risk: such a finding has important prognostic implications. For this reason, dysplasia should be confirmed by an experienced pathologist, because interobserver variation for the detection of dysplasia is high.<sup>106–108</sup> Furthermore, individual studies that do not show an increased risk of malignant transformation in low-grade dysplasia<sup>109</sup> need to be placed in the context of the meta-analysis.

### 9.4.2. Dysplasia and colectomy

#### ECCO Statement 9J

High grade dysplasia in flat mucosa and adenocarcinoma are indications for proctocolectomy [EL2, RG B]. A patient with low-grade dysplasia in flat mucosa should be offered proctocolectomy or repeat surveillance biopsies within 3–6 months [EL2b, RG B]

Once dysplasia is found, the rationale of such a surveillance programme demands that colectomy is performed, because the risk of CRC is appreciably increased.<sup>105</sup> If high grade dysplasia is present, the decision is easier, because the risk of concomitant CRC may be as high as 32%,<sup>106</sup> assuming that the biopsies were indeed obtained from flat mucosa and not from an adenoma. If low-grade dysplasia is detected, the 9-fold increased risk of developing CRC reported in the most recent meta-analysis<sup>105</sup> could reasonably be viewed as justification for colectomy as well, and this option should be discussed with the patient.<sup>110</sup> However, because some follow-up studies of patients with low-grade dysplasia have shown a low rate of CRC development,<sup>86,111</sup> it seems a reasonable compromise to continue surveillance with extensive biopsy sampling at shorter (perhaps 3–6 month) intervals in those who will adhere strictly to the surveillance program. This remains controversial in the literature and was discussed during the conference as well.<sup>66,112</sup>

### 9.4.3. Dysplasia and raised lesions

#### ECCO Statement 9K

A raised lesion with dysplasia should be completely resected. In the absence of dysplasia in the flat surrounding mucosa, meticulous endoscopic surveillance should be proposed [EL2b, RG B]. If endoscopic resection is not possible or if dysplasia is found in the surrounding flat mucosa, proctocolectomy should be recommended [EL2b, RG B]

Raised lesions on a background of UC have been traditionally referred to as “Dysplasia Associated Lesion or Mass” or DALM. Until recently this finding has been considered an absolute indication for colectomy. It is increasingly recognised, however, that some of these raised lesions may resemble sporadic adenomas and that they may be amenable to complete endoscopic resection.<sup>97,113–115</sup> If the polypectomy is confirmed complete by histology and if biopsies obtained

from the flat mucosa immediately adjacent to the polypectomy site show no dysplasia and if, in addition, no dysplasia is found elsewhere in the colon, then colectomy may be safely deferred. Careful follow-up, preferably with surveillance colonoscopy at 3 months and then 6 monthly, is needed if this strategy is followed, because at least half of such patients in the four studies quoted developed further raised lesions. If the lesion does not resemble typical adenoma, is not respectable, or is associated with dysplasia in the adjacent mucosa, then colectomy is indicated due to the high risk of concomitant CRC.<sup>90,113</sup>

## 9.5. Chemoprevention

The risk of developing CRC has been shown to be higher in patients with persistent mucosal inflammation,<sup>73</sup> and thus appropriate therapy may reduce the risk of CRC associated with chronic UC. Several studies suggest that sulfasalazine or mesalazine may lead to a risk reduction, referred to as a chemoprotection. Velayos et al. performed a meta-analysis that included 334 cases of CRC, 140 cases of dysplasia and a total of 1932 subjects extracted from 3 cohort studies and 6 case-control studies.<sup>79</sup> This suggested that in a population matched for extent and duration of UC, aminosalicylates may reduce the risk of colorectal cancer. The risk reduction was significant for CRC development (OR 0.51, 95% CI 0.37–0.69), but not for dysplasia (OR 1.18, 95% CI 0.41–3.43). In view of the low toxicity of mesalazine and considering that the number of patients needed to treat (NNT) to prevent one CRC may be as low as 7 in patients with 30 years of disease,<sup>116</sup> the Consensus felt that such a therapy should be considered and potentially offered to all UC patients in the absence of contraindications. The limitations of the data are, however, recognised and some large studies have shown no benefit.<sup>78</sup> When 76 cases of CRC and UC in a cohort of 18,969 patients in the UK General Practice Research Database were compared to six matched control cases, regular users of 5ASA (defined as six or more prescriptions in the preceding 12 months) had a trend towards a lower risk of CRC compared with irregular users (unadjusted OR 0.7, 95% CI 0.44–1.03). For mesalazine, but not sulfasalazine, the effect was significant depending on the total number of prescriptions: OR 1.13 (0.49–2.59) for 6–12 prescriptions, OR 0.30 (0.11–0.83) for 13–30 prescriptions and OR 0.31 (0.11–0.84) for >30 prescriptions.<sup>117</sup>

Patients with UC-associated PSC appear to be at particularly high risk of developing CRC.<sup>75</sup> In follow-up to a randomised trial evaluating the benefit of ursodeoxycholic acid in these patients, patients assigned to active medication for their biliary disease had a lower incidence of dysplasia and CRC development compared to patients assigned to placebo.<sup>118</sup> This study confirmed prior data from a cross-sectional study<sup>119</sup> in the setting of a prospective randomised trial. The Consensus considered these data sufficient evidence to recommend this therapy in all patients with UC and PSC, considering the potential benefit of the drug on both conditions and low toxicity. Nevertheless, the limitations of the data are again recognised, since not all studies have identified an association between PSC and CRC in patients with UC.<sup>79</sup> Interestingly, when the same group examined population-based as opposed to hospital-based cohorts, a significant association between PSC and CRC was identified (OR 6.9, 95% CI 1.2–40), although a protective

effect of aminosalicylates could not be discerned (cumulative dose of sulfasalazine (OR per kg 1.1, 95% CI 1.0–1.3) and mesalazine (OR per kg 1.3, 95% CI 0.9–1.9).<sup>78</sup>

### ECCO Statement L

Chemoprevention with 5-ASA compounds may reduce the incidence of colorectal cancer in UC patients and should be considered for all UC patients [EL2, RG B]. Colorectal cancer chemoprevention with ursodeoxycholic acid should be given to patients with PSC [EL1b, RG B]

## 9.6. Prognosis

The prognosis of CRC complicating UC has generally been considered worse than for sporadic CRC. This may not be valid. In a report from the Mayo Clinic, 290 patients with IBD-associated CRC (241 with chronic ulcerative colitis and 49 with Crohn's disease) were matched with an equal number of age- and sex-matched sporadic CRC patients between 1976 and 1996. 55% of IBD-related tumours were distal to the splenic flexure compared to 78% of sporadic CRC, but during a median follow-up period of 5 years, 163 IBD-associated CRC patients died (56%), compared with 164 sporadic CRC patients (57%). The 5-year survival rates were 54% in the IBD-CRC subgroup vs. 53% in the sporadic CRC subgroup ( $p=0.94$ ).<sup>120</sup> This is not that dissimilar to experience from St Mark's Hospital. In the largest experience of surveillance colonoscopy in 600 patients during 5932 patient-years of follow-up, 30 patients (5%) developed CRC, with a 5-year survival rate of 73.3%.<sup>69</sup>

The prognosis of colorectal dysplasia in IBD is also debated (Section 9.4.1). In a population-based study from Minnesota, 29/725 (4%) IBD patients developed flat dysplasia ( $n=8$ ), a Dysplasia Associated Lesion or Mass (DALM,  $n=1$ ), or an adenoma-associated lesion or mass (ALM  $n=18$ ) in an area of IBD, or an ALM outside the area of IBD ( $n=2$ ). Among 6 patients with flat low-grade dysplasia (fLGD) who did not undergo colectomy, none progressed during a median of 17.8 (range 6–21) years of observation with a median of 3 (range 0–12) surveillance colonoscopies. Four (22%) patients with ALMs in areas of IBD who did not undergo surgery developed low-grade dysplasia or DALMs. Dysplasia located proximal to the splenic flexure was significantly associated with a risk of recurrence or progression of dysplasia. This population-based cohort did not confirm an increased risk of cancer related to flat low-grade dysplasia,<sup>78</sup> which is at odds with the meta-analysis.<sup>105</sup>

## 10. Children and adolescents

### 10.1. Introduction

About 10–15% of patients with inflammatory bowel disease are diagnosed before the age of 18 years.<sup>121</sup> During puberty the incidence is 7 per 100 000 per year and increases further during adolescence to about 12 per 100 000 at age 20–29, consistent with a peak around the age of 30 years.<sup>122</sup> In children most cohort studies show a lower incidence of ulcerative colitis (UC) compared to Crohn's disease (CD),<sup>123</sup> but the incidence of CD has clearly increased over the past

decade. In contrast, the incidence of UC is stable in some studies,<sup>124–126</sup> but increasing in other cohorts.<sup>127–129</sup> The median age of onset of symptoms in UC is 12 years in most paediatric studies,<sup>122,130,131</sup> but the diagnostic delay is considerably shorter than for CD. In contrast to adults, the clinical presentation of UC is often more severe in children, which may be explained by the predominance of pancolitis (70–80% of children) at the time of diagnosis.<sup>131,132</sup>

## 10.2. Diagnosis

### 10.2.1. Diagnostic threshold

#### ECCO Statement 10A

Ulcerative colitis should be suspected in a child with chronic ( $\geq 4$  weeks) or recurrent ( $\geq 2$  episodes in 6 months) bloody diarrhoea, after exclusion of infective or other causes. This applies particularly when there is growth failure and/or pubertal delay, a family history of IBD, increased markers of inflammation, or if anaemia is present [EL2b, RG B]

In contrast to paediatric CD and its diverse symptomatology, the clinical manifestation of UC is almost uniformly bloody diarrhoea (84–94% of children), accompanied by tenesmus.<sup>132</sup> Although an infective aetiology should be excluded, its presence does not exclude a diagnosis of UC or CD. The combination of rectal bleeding, anaemia and increased ESR identified 86% of patients with IBD prior to an endoscopic procedure.<sup>133</sup> Other retrospective case series have confirmed the diagnostic value of increased inflammatory markers and anaemia for IBD.<sup>134,135</sup>

A shorter interval from symptoms to diagnosis of UC probably explains why growth failure is half as common compared to CD. As with adults, the greatest risk factor for developing UC in childhood is to have a family member with ulcerative colitis (relative risk 7–17).<sup>137,138</sup> The risk for CD in a family member with Crohn's disease is a relative risk of 15–35. The stronger the family history, the earlier the onset of symptoms. For patients with early-onset UC (<5 years' age), 26%–44% have a family history of UC, compared to older patients or children with CD.<sup>139,140</sup> Genetic factors are likely to have a stronger influence in paediatric IBD, especially in early-onset acute severe UC, compared to older children or adults.<sup>141,142</sup> Nevertheless, most children with IBD have no family history and are considered sporadic.

### 10.2.2. Documentation

#### ECCO Statement 10B

In all children with UC, the height, weight (and pre-diagnosis growth curve) and pubertal stage, should be recorded at diagnosis, and regularly during follow-up [EL3b, RG B]

Growth failure is a unique complication of paediatric IBD, caused by a combination of inadequate calorie intake, increased losses and active inflammation. Efficacy of medical treatment and concomitant mucosal remission is characterised by normal linear growth and pubertal development. In contrast, when catch-up growth does not occur after growth failure at

diagnosis, or when height velocity decreases during maintenance treatment, it is highly likely that there is persistent disease activity, so therapy should be more aggressive and an adequate calorie intake ensured.<sup>136,143,144</sup>

### 10.2.3. Diagnostic procedures

#### ECCO Statement 10C

Ileocolonoscopy and biopsies should be performed in all children or adolescents with a suspicion of inflammatory bowel disease (IBD). Upper gastrointestinal endoscopy is recommended when ileocolonoscopy does not confirm a diagnosis of ulcerative colitis [EL2a, RG B]

#### ECCO Statement 10D

In children and adolescents (up to 16–18 years of age), endoscopy should be performed by a specialist with experience in paediatric gastroenterology, preferably by a paediatric gastroenterologist [EL 5, RG D], in a setting that is suitable for diagnosing and treating children with IBD (paediatric hospital, with access to general anaesthesia)

The IBD working group of the European Society of Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) has reached a consensus on the diagnosis of IBD in children, which has been summarised in the 'Porto Criteria'.<sup>145</sup> This group feels it essential to establish a diagnosis of the type of disease, as well as to determine severity, localisation, and extent of the disease, before treatment is started. Paediatric patients with UC have more extensive disease and rectal sparing in up to 30%,<sup>146</sup> so a complete diagnostic work-up is warranted in children with bloody diarrhoea. Evidence supporting colonoscopy with ileal intubation and multiple biopsies, rather than sigmoidoscopy alone, is provided by retrospective cohort studies.<sup>146–148</sup> In cases with extensive colitis that cannot be classified, gastro-duodenoscopy may allow definitive diagnosis.<sup>149</sup>

The ECCO Consensus agrees that a paediatric gastroenterologist, rather than a specialist in adult endoscopy, should best perform endoscopy in children suspected of IBD. The most important argument is quality of care, particularly because endoscopy in children is preferably done under general anaesthesia: this is preferred for reasons of comfort and care and has been shown to be safe.<sup>150–155</sup> Moreover, the treatment and follow-up of children and adolescents with IBD should be in the hands of a paediatric gastroenterologist who is aware of age-related differences in disease presentation and treatment. Such specialists are experienced in handling problems such as linear growth retardation and pubertal delay.<sup>156</sup>

## 10.3. Induction therapy in children

### 10.3.1. Distal colitis

#### ECCO Statement 10E

Oral [EL2b,RGB] aminosalicylates and/or topical aminosalicylates (suppositories in proctitis, enemas in left-sided colitis) [EL5, RGD] are appropriate initial induction therapy for mild to moderate distal colitis in children or adolescents

No studies have been performed in children with distal colitis. A questionnaire sent to members of the IBD working group of ESPGHAN, however, revealed great variation of care in the treatment of distal colitis. The first choice was either oral treatment alone (mesalazine 21%, sulfasalazine 36%), or in combination with topical treatment (mesalazine 36%, corticosteroids 7%). Considering the rarity of proctitis in children, no standard treatment protocols exist.

### 10.3.2. Extensive colitis

#### ECCO Statement 10F

For mild to moderate pancolitis in children, oral mesalazine/sulfasalazine is recommended as first line therapy [EL2b, RG B]. Oral steroids are appropriate if the response is insufficient [EL4, RG D]

Only one prospective study has confirmed the efficacy of oral aminosalicylates in children with active ulcerative colitis.<sup>157</sup> In this trial, a clinical response at 8 weeks was seen in 79% of patients receiving sulfasalazine (60 mg/kg/day) and 50% of patients on olsalazine (30 mg/kg/day). Retrospective studies have also shown that oral aminosalicylates effectively induce clinical remission.<sup>158–162</sup>

Although sulfasalazine may cause more gastrointestinal side-effects, it is the preferred aminosalicylate treatment in young children who cannot swallow tablets, because it is available as a suspension. Alternatively, mesalazine can be given as an enteric-coated granule formulation. Based on expert opinion and extrapolation from pharmacokinetic studies,<sup>159,161,163</sup> the advised dose (oral and rectal mesalazine combined) in children aged 12 years or older of mesalazine, is 50–75 mg/kg/day with a maximum of 4 g/day. For sulfasalazine it is 100 mg/kg/day with a maximum of 6 g/day.

Concerning oral corticosteroids, no studies have been performed in children with UC. Nevertheless, prospectively collected data from the US Pediatric Inflammatory Bowel Disease Collaborative Research Group Registry database provides a useful insight.<sup>164</sup> In 97 children (age <16 yr) with newly diagnosed UC between 2002 and 2005, with a minimum of 1 year of follow-up, 79% received corticosteroids, most (62/77) within 30 days of diagnosis. For those treated within 30 days, disease activity at 3 months was inactive in 60%, mild in 27%, and moderate or severe in 11%. At 12 months, 31 of 62 (50%) of the early corticosteroid-treated patients were considered corticosteroid responsive and 28 (45%) were corticosteroid-dependent. A total of 4 patients receiving corticosteroids required colectomy in the first year. Immunomodulators were used in 61% of all corticosteroid-treated patients. This is similar to adults: early response is excellent, but dependence is common, even with immunomodulators. Evaluation among the IBD working group of ESPGHAN demonstrated that 46% favoured addition of corticosteroids if response to aminosalicylates was found to be insufficient. Oral prednisolone is given as a once daily dose of 1–2 mg/kg/day, with a maximum dose of 40 mg, for 2–4 weeks (until clinical remission), then tapered to zero in 6–8 weeks. Although not supported by clinical evidence from randomised clinical trials, calcium and vitamin D are usually supplemented during a course of steroid treatment.

### 10.3.3. Severe colitis

#### ECCO Statement 10G

For severe pancolitis in children, corticosteroids are first line therapy [EL4, RG D]. If the response is insufficient, intravenous ciclosporin [EL4, RG C] or infliximab [EL4, RG C], or colectomy are appropriate options

Although no randomised clinical studies have been performed in children with acute severe UC, all respondents to the ESPGHAN questionnaire agreed that corticosteroids are the first line therapy in severe pancolitis. In a meta-regression of response to steroids in 32 studies involving 1991 patients (1974–2006), only 43 children were included.<sup>165</sup> To evaluate the outcome in children, a retrospective study of 74 admissions in 63 children (57% males, age at diagnosis 10.9±4 yr, 79% extensive colitis) treated at Toronto SickKids Hospital 1995–99 was performed.<sup>166</sup> 41% failed intravenous steroids by discharge and 23 (37%) came to colectomy on that admission. By one year, 54% and by 5 yr 59% had come to colectomy. There was no clear consensus from ESPGHAN as to whether corticosteroids should be given as the only treatment (25% of respondents), or in combination with oral mesalazine (25%), or intravenously with adjunctive parenteral nutrition (50%). Given the similarity in the response of children to steroids compared to adults (Section 5.2.4, preceding paper same issue), it seems unlikely that mesalazine is necessary. Although nutritional support is particularly appropriate in children, TPN in adults has not been shown to offer any advantage when managing acute severe colitis (Section 5.2.4, preceding paper same issue).

When 3–5 days of intravenous corticosteroids are ineffective, rescue therapy with ciclosporin, tacrolimus, or infliximab are the only two options to avoid or postpone colectomy. An objective assessment of the response to steroids facilitates management as it does in adults (see Section 5.2.5, preceding paper same issue). A paediatric index of severity as been developed<sup>166</sup> and when calculated on day 3, strongly predicts failure of intravenous steroids.<sup>167</sup> As with adults, stool frequency ( $p=0.001$ ) and CRP ( $p=0.045$ ) on day 3 (but not day 1) predict failure, along with temperature ( $p=0.001$ ). Case studies with intravenous ciclosporin in children with severe, steroid-refractory colitis who are candidates for surgery, have shown remission of the disease in up to 80% of cases.<sup>168–172</sup> In many children, however, tapering of oral ciclosporin resulted in a relapse and was followed by colectomy within a year of cessation of treatment. In occasional patients, short term ciclosporin treatment can effectively induce remission while waiting for azathioprine maintenance treatment to take effect.<sup>170</sup>

Infliximab has not been studied prospectively, but small retrospective studies in new-onset steroid-refractory patients show complete remission in 75–88% of patients.<sup>173–175</sup> With the small numbers of patients studied and limited follow-up, it is currently unknown whether infliximab therapy is effective in avoiding colectomy, or whether it simply defers it. The Consensus view is that rescue therapy with either ciclosporin, tacrolimus, or infliximab should only be initiated in a specialist centre where a paediatric and/or colorectal surgeon are available and involved in the treatment of these severely sick children.

## 10.4. Maintenance therapy in children

### ECCO Statement 10H

Oral mesalazine or sulfasalazine are recommended maintenance treatment in the same dose as for induction therapy [EL5, RG D]. For difficult patients with extended and/or relapsing disease, who are steroid-refractory or steroid-dependent, azathioprine/mercaptopurine is recommended [EL4, RG C]. Long-term steroids are contraindicated and ciclosporin is inappropriate

### 10.4.1. Aminosalicylates

The efficacy of mesalazine or sulfasalazine maintenance treatment has not been studied in children with UC. From the IBD working group of ESPGHAN questionnaire respondents, 57% advised continuing the same mesalazine dose as used for induction, while 43% advised a lower dose. The Consensus view is based on results from adult studies that indicate that high dose 5-ASA is effective maintenance treatment. Long-term corticosteroids are absolutely contraindicated, because they do not maintain remission and have a negative effect on linear growth and bone mineralisation. Ciclosporin maintenance treatment is ineffective and inappropriate, because serious, sometimes irreversible, side-effects may occur.

### 10.4.2. Thiopurines

Retrospective cohort studies have demonstrated that maintenance with azathioprine/mercaptopurine is effective, while achieving a steroid-sparing effect.<sup>176–179</sup> This steroid-sparing effect is more evident when azathioprine treatment is started early in the course of disease, within 2 years after diagnosis.<sup>179</sup> The advised dose for azathioprine in children is 2–3 mg/kg/day and that for mercaptopurine is 1–1.5 mg/kg/day.

## 10.5. Surgery in children

### ECCO Statement 10I

Colectomy is indicated for severe colitis with acute complications not responding to medical therapy; persistently active disease with failure or toxicity of medical treatment; failure to taper corticosteroid treatment despite immunosuppressant use; growth retardation or pubertal delay despite medical treatment [EL 4, RG C]

### 10.5.1. Indications

In acute severe colitis, the decision to perform colectomy should be evaluated on a day-to-day basis by both the medical and surgical team. If the disease is not responding to 7–10 days of either calcineurin inhibitors (ciclosporin, tacrolimus) or infliximab, colectomy is indicated.

Colectomy is also indicated for persistently active disease, when corticosteroid dependency exists despite concomitant therapy with azathioprine/mercaptopurine, or when immunosuppressive treatment has side-effects. Growth failure despite apparently adequate maintenance therapy is also an indication for colectomy, even when clinical symptoms appear

mild.<sup>180–184</sup> Preliminary (and anecdotal) experience with infliximab in children suggests that it may be more effective in acutely ill patients, compared to patients with chronic refractory disease.<sup>173,175,185</sup> It rarely achieves steroid-free remission. Therefore, infliximab cannot be recommended for chronic steroid-dependent disease in children.

### 10.5.2. Procedures

### ECCO Statement 10J

Colectomy should be performed by an experienced paediatric surgeon, ideally with the assistance of a colorectal surgeon with paediatric experience; ileo-pouch-anal anastomosis (IPAA) should only be performed in a highly specialised centre [EL 4, RG C]

Depending on the local circumstances, a child needing colectomy should be referred for expert care at a specialist centre. Case series of IPAA in children show good results in terms of quality of life, continence and incidence of pouchitis.<sup>181,182,186–189</sup> However, in very young children (<10 years), pouchitis is reported in 75% of the patients.<sup>190</sup> Because IPAA decreases female fecundity,<sup>191,192</sup> colectomy with ileorectal anastomosis until later IPAA may be a better option in girls.<sup>193</sup> Expert advice should be sought.

## 10.6. Nutritional support

### ECCO Statement 10K

Enteral or parenteral nutritional therapy is inappropriate primary treatment. However, a nutritional evaluation is essential and nutritional support should be provided when required [EL5, RG D]

### ECCO Statement 10L

There is no indication for a “special diet” for ulcerative colitis, because none are effective and there is a risk of nutritional deficiencies [EL5, RG D]

It has not been shown that enteral nutrition has a primary therapeutic role in ulcerative colitis. There are many theories that suggest that diet may be implicated in the aetiology of inflammatory bowel disease. However, there is, as yet, no dietary approach proven to reduce the risk of developing IBD. Children with IBD have increased calorie and protein requirements, so intake should be at least 120% of recommended daily allowances (RDA). If oral intake is poor due to anorexia during a period of disease activity, high-calorie supplements may be indicated and specialist dietetic advice is appropriate.

## 10.7. Psychosocial support

### ECCO Statement 10M

Psychosocial support is important adjunctive treatment, because depressive symptoms are frequent and psychosocial support may be associated with a better outcome and a better quality of life [EL3b, RG B]

Children and adolescents with IBD are at greater risk of developing behavioural difficulties or emotional dysfunction and depression in particular (in almost 25% of patients), as well as anxiety, social dysfunction and low self-esteem compared to healthy children.<sup>194–197</sup> The quality of life in adolescents with IBD is generally lower than healthy controls.<sup>198–201</sup> Two large randomised studies have demonstrated that psychosocial support by a patient-orientated self-management approach can have a beneficial influence on the course of disease.<sup>202,203</sup> Therefore, appropriate medical information and mental health support are recommended, because this may influence disease activity.<sup>195</sup>

## 10.8. Transition of care to adult services

### ECCO Statement 10N

Transitional clinics represent optimal care and are highly recommended [EL5, RG D]

A careful transition of patients from the paediatric service to adult gastroenterologists is vital, because it may reinforce treatment adherence and improve quality of life.<sup>204</sup> There are many differences between paediatric and adult care. In the paediatric service, children and adolescents with IBD are usually seen together with their parents and often receive more attention, because the disease is uncommon in children compared to adults. A paediatric specialist nurse may be on hand to advise and be a point of contact for the child or parents. Endoscopy is performed under general anaesthesia, whereas this is exceptional in adults. On the other hand, the paediatric gastroenterologist rarely discusses long-term issues, such as cancer risk or surveillance. Close collaboration between the paediatric and adult services will overcome these differences. The ideal setting for this is a transitional clinic where adolescent patients are seen by both specialists.<sup>205</sup> The alternative is to establish a parallel clinic, where paediatric and adult IBD clinics run independently but at the same time, so that when a suitable patient is seen, it is then a simple matter for the paediatric or adult gastroenterologist to go down the corridor to contact their opposite number so that the young person can be introduced or seen together. A trained IBD nurse specialist can play an important role coordinating care between the service, the patient and the family during the transitional period.

## 11. Pregnancy

The section on pregnancy and ulcerative colitis will be published subsequently. The principles of managing pregnancy, delivery, breast-feeding and Crohn's disease also apply to ulcerative colitis.<sup>206</sup> See also Cornish J, Tan E, Teare J, et al. A meta-analysis on the influence of inflammatory bowel disease on pregnancy. *Gut* 2007;**56**:830–7.

## 12. Psychosomatics

### 12.1. Introduction

While psychosocial factors are generally considered important in ulcerative colitis, controversy still exists about their role. This leads to potential inconsistencies in clinical practice. A biopsychosocial model<sup>207,208</sup> represents an advantage over a

biomedical model, because it embodies the complex biological and psychosocial interactions that explain human illness or its effects. Attention to psychosocial factors associated with ulcerative colitis may have consequences not only on psychosocial well-being and quality of life, but also on the activity of the disease itself. The key words used in the systematic literature review of Medline and Embase for this review were ulcerative colitis as well as inflammatory bowel disease and irritable bowel syndrome – psychology; psychosocial; psychotherapy; quality of life; doctor patient relationship; and psychopharmaceuticals.

## 12.2. Influence of psychological factors on disease

### 12.2.1. Aetiology

#### ECCO Statement 12A

A speculated association between psychological factors and the aetiology of ulcerative colitis cannot be proven. There is, however, an influence of psychological distress and mood disorders on the course of the disease [EL1b, RG B]

Studies about the influence of psychological factors on the development of ulcerative colitis are very limited. There are a few studies with hypothetical interpretations about the influence of psychosocial factors on the aetiology of the disease.<sup>209–212</sup> Many studies on psychosocial factors relate to inflammatory bowel disease (IBD) rather than ulcerative colitis or Crohn's disease in particular.

### 12.2.2. Pattern of disease

#### ECCO Statement 12B

There is evidence of an interaction between psychological factors and IBD activity. Depression and perceived chronic distress represent risk factors for relapse of the disease. It remains controversial whether acute life events trigger relapses [EL 1b, RG B]. Most patients consider stress to have an influence on their illness [EL 4, RG C]

Psychological factors are considered to have an influence on the course of the disease, which is consistent with evidence in the recent literature about the influence of subjective perceived psychological distress on disease activity of ulcerative colitis.<sup>213–217</sup> Studies about the influence of major life events on the biological disease activity have yielded contradictory results.<sup>218–220</sup> Patients themselves and the majority of European experts at the Consensus conference consider psychosocial distress as influencing the risk of relapse.<sup>221,222</sup> One study shows a heightened response to stressors and the greater epithelial damage in IBD patients, which suggests that stress-induced activation of the brain-gut axis and of mucosal mast cells may be important in the initiation and/or flare up of IBD.<sup>223</sup>

## 12.3. Psychological disturbances in ulcerative colitis

#### ECCO Statement 12C

Psychological disturbances seem to be a consequence of the illness rather than the cause of, or specific to ulcerative colitis. The degree of psychological distress and disturbances correlates with the disease severity, predicts health-related quality of life and influences the course of disease [EL 1b, RG B]

**ECCO Statement 12D**

Clinicians should particularly assess depression among their patients with active disease and those with abdominal pain in remission [EL 2b, RG B]

Patients with ulcerative colitis seem to have no more, or only slightly more, psychological disturbances compared to patients with other chronic diseases.<sup>211,224–229</sup> A consistent association between psychological factors and the prevalence of IBS-like symptoms in patients in remission has been reported.<sup>229–232</sup> There is also evidence that children and adolescents with IBD comprise a population at high risk of developing a psychiatric disorder.<sup>233,234</sup> A recent study with a large IBD population has shown that IBD patients experience a rate of depression that is triple that of the general population (16.3% vs. 5.6%).<sup>235</sup> In this study 17% of depressed patients had considered suicide in the past 12 months and an additional 30% had considered suicide at an earlier time. In individuals who were currently depressed, female patients were more likely than males ever to have considered suicide (50% vs. 31%). Depressive coping strategies are positively associated and predict health-related quality of life.<sup>236</sup> Furthermore, the psychosocial consequences of the illness become more significant with increasing severity of the disease and quality of life is related to disease activity, symptoms<sup>218,224,237–243</sup> and female gender.<sup>237,244,245</sup>

## 12.4. Approach to psychological disorders

### 12.4.1. Communication with patients

**ECCO Statement 12E**

The psychosocial consequences and health-related quality of life of patients should be taken into account in clinical practice at regular visits. Individual information and explanation about the disease should be provided through a personal interview. The course of the disease can be improved by combining self-management and patient-centred consultations [EL 1b and 3b, RG B]

Health perceptions impact on the experience of the illness.<sup>226</sup> Increasing physician awareness of the fact that psychologically distressed patients have difficulty in processing clinically relevant information<sup>246</sup> may lead to improved doctor–patient communication.<sup>247</sup> It is important that patients are informed about their condition through an individual interview, in conjunction with emotional support. This is because a lower level of information is associated with greater concern,<sup>248</sup> despite the impression of some doctors that more information increases the level of anxiety. Psychosocial factors are strongly correlated with health care utilization.<sup>249</sup> Self-management guidebooks together with patient-centred consultations improve patients' disease control.<sup>250,251</sup> It should however be recognised that educational booklets on their own do *not* seem to be helpful and may even worsen the health-related quality of life of patients attending tertiary centres.<sup>252</sup> In addition, patient education programmes seem to have very limited or even *no* influence on the course of their illness, their health-related quality of life, or their psychological affect.<sup>253–255</sup> Almost all

experts at the Consensus (91%) are convinced that a good doctor–patient relationship is helpful psychologically and take psychosocial factors into account for both diagnosis and therapy. Most experts at tertiary centres have the opportunity for integrated somatic and psychological care of patients. However, patients describe deficiencies in the care of family members, insufficient information and inadequate access to healthcare resources.<sup>256</sup>

### 12.4.2. Psychological support

**ECCO Statement 12F**

Physicians should assess the patient's psychosocial status, quality of life and demand for additional psychological care and recommend psychotherapy if indicated. Integrated psychosomatic and gastroenterology care should be available [EL 2b, RG B]. Patients should be informed of the existence of patient associations [EL 5, RG D]

For assessment of quality of life, two validated IBD-specific questionnaires have been shown to be sensitive, reproducible and responsive for use in clinical trials: the Inflammatory Bowel Disease Questionnaire (IBDQ)<sup>257</sup> and the Rating Form of Inflammatory Bowel Disease Patient Concerns (RFIPC).<sup>258</sup> Detection and treatment of psychological distress has the potential to improve health-related quality of life.<sup>259</sup> The presence of psychological disorders contributes to poor quality of life and the number of doctor visits, regardless of the severity of the condition.<sup>249</sup> This is the common experience of doctors caring for patients with IBD, even if the potential or need to treat this aspect of the illness is perceived.

To assess the demand for psychological care in chronic diseases, a validated questionnaire is available, developed and based on inflammatory bowel disease.<sup>260</sup> Most experts (80%) feel themselves able to recommend psychotherapy during a discussion with patients. There is no study on their competence at doing this, but this is consistent with the experience of participants in the European Consensus on the management of Crohn's disease,<sup>206</sup> the German Consensus on Crohn's disease,<sup>56</sup> and that on ulcerative colitis.<sup>261,262</sup> Since strategies aimed at improving social support can have a favourable impact on psychological distress,<sup>263</sup> training of gastroenterologists to integrate psychosocial factors in clinical practice should be taken into consideration.

### 12.4.3. Therapeutic intervention

**ECCO Statement 12G**

Psychotherapeutic interventions are indicated for psychological disorders associated with ulcerative colitis [EL 1b, RG B]

Psychotherapy and relaxation methods have a positive influence on IBD, mainly affecting the psychological dimensions of the illness such as psychological well-being, coping strategies and psychological distress,<sup>264–268</sup> as well as perception of pain.<sup>269</sup> This underpins the recommendation (Statement 12G). The diagnosis of ulcerative colitis is insufficient alone to recommend psychotherapy, since studies of psychotherapy on patients without psychological

disturbance show little or no benefit.<sup>270</sup> One study that combined patients with Crohn's disease and ulcerative colitis reported an influence of psychotherapy on disease activity, but there was inhomogeneity in randomisation of the treatment and control groups, so the results are not included in the evidence-based recommendation.

#### 12.4.4. Therapeutic choice

##### **ECCO Statement 12G**

The choice of psychotherapeutic method depends on the psychological disturbance and should best be made by specialists (Psychotherapist, Specialist for Psychosomatic Medicine, Psychiatrist). Psychopharmaceuticals should be prescribed for defined indications [EL 5, RG D]

There is no evidence that one psychotherapeutic method should be preferred over another. Relaxation exercises are useful, since they are easy to learn and perform. Expert opinion believes that there is an advantage if the psychotherapist has experience in the treatment of patients with chronic inflammatory bowel diseases and works closely with the patient's gastroenterologist. There are no specific studies on the use of individual psychopharmaceuticals in ulcerative colitis.<sup>271</sup> In spite of this, almost all experts believe that there are clinical situations in which antidepressants should be recommended for treatment of psychological distress associated with ulcerative colitis.

### 13. Extraintestinal manifestations

#### 13.1. Introduction

Extra-intestinal manifestations (EIMs) occur in up to 30% of patients affected by ulcerative colitis or Crohn's disease,<sup>272–274</sup> although it is probable that studies from referral centres have over-estimated the prevalence and community studies suggest that their prevalence may be much lower. What is interesting is that the occurrence of one EIM appears to predispose to others. This suggests an underlying generic susceptibility in some patients that is largely genetically determined, although may yet be prone to environmental influence. Female patients with colitis (either ulcerative or Crohn's colitis) appear to be particularly susceptible.<sup>275</sup>

Scoring systems such as the Crohn's disease activity index (CDAI) include EIMs in the assessment. This is a weakness, although not widely recognised, since only some EIMs are related to disease activity and a genetic susceptibility in a minority of patients introduces bias. Those EIMs broadly related to the activity of colitis include oligoarticular peripheral arthritis, erythema nodosum, oral aphthous ulcers and episcleritis.<sup>274</sup> Polyarticular peripheral arthritis, pyoderma gangrenosum [PG], uveitis and spondylarthropathy tend to pursue a course independent of disease activity, while primary sclerosing cholangitis [PSC] is most prevalent in patients with colitis that follows an apparently mild course.

For those EIMs closely related to ulcerative colitis activity, treatment can parallel that of the underlying disease. Treatment otherwise is mainly on a case-by-case basis as randomised controlled trials are mostly lacking. Specific

therapy for EIMs is strongly influenced by current IBD treatment, and may include increasing dosage of existing drugs or the addition of new agents.

Consensus review indicates that gastroenterologists will be comfortable diagnosing and treating the more common extraintestinal manifestations, unless they prove resistant, with the exception of eye involvement for which the advice of an ophthalmologist is selected in a great majority of cases (93%). It is noted however that the frequency with which routine dermatological (46%) and rheumatological (31%) advice would be sought has increased since the review panel was interrogated on their approach to EIMs of Crohn's disease in 2004.<sup>206</sup> This section concentrates on the more frequently encountered EIMs, for which at least some quantifiable data exist. Thrombotic complications of colitis and their prevention are considered in the section on acute management of colitis. Anaemia in colitis (as in Crohn's disease) is too frequently neglected: authoritative guidelines have been published separately.<sup>276</sup>

#### 13.2. Arthropathies

##### **ECCO Statement 13A**

Diagnosis of non-axial arthritis and arthropathy associated with UC is made on clinical grounds based on characteristic features and exclusion of other specific forms of arthritis [EL3b, RG C]. Type I is pauciarticular and affects large joints acutely at times of UC activity. Type II is polyarticular, affecting a larger number of peripheral joints independently of UC activity [EL 2b, RG B] Axial arthritis, including sacroiliitis and ankylosing spondylitis, is diagnosed on conventional rheumatological grounds, and is supported by characteristic radiological changes, magnetic resonance imaging being the most sensitive [EL2b, RG B]. Although HLA B-27 is over-represented in axial arthritis related to UC this is not of diagnostic value [EL2b, RG B]

The diagnosis of non-axial arthritis and arthropathy associated with inflammatory bowel disease (IBD) is made on clinical grounds and two types have been defined by the Oxford group. The distinction is supported by differences in genetic susceptibility.<sup>277</sup> Type I is a large joint pauciarticular arthropathy that occurs at times of IBD activity, while type II is a polyarticular small joint arthropathy, whose activity is largely independent of IBD activity. Axial arthritis includes sacroiliitis and ankylosing spondylitis which are diagnosed clinically, supported by characteristic radiological changes. Magnetic resonance imaging is the diagnostic tool of choice.

##### 13.2.1. Pauciarticular peripheral arthropathy

Type I arthropathy<sup>277</sup> predominantly affects weight-bearing joints, including the ankles, knees, hips, wrists, elbows and shoulders. Pauciarticular means that fewer than five joints are affected. The arthritis is usually acute, self-limiting, resolves within weeks as disease activity decreases, and leaves no permanent joint damage. Clinical examination reveals painful, tender, swollen joints. Aspiration is unnecessary unless an alternative diagnosis is suspected. The differential diagnosis includes osteoarthritis, septic arthritis, pyrophosphate arthropathy, coincidental rheumatoid



arthritis, or occasionally, gout. If just one hip joint is affected then steroid-induced osteonecrosis should be considered.<sup>279</sup>

### 13.2.2. Polyarticular peripheral arthropathy

Type II arthritis predominantly affects the small joints of both hands as a symmetrical arthropathy. Pain is commonly disproportionate to the signs of arthritis. It usually persists for months or years and follows a course independent of IBD activity. It may persist after colectomy or start after ileo-pouch-anal anastomosis. The differential diagnosis includes osteoarthritis, but also includes treatment side-effects such as steroid-induced pseudorheumatism (which is common after withdrawal of long-term steroids) and mesalazine- or azathioprine-induced arthropathy.<sup>278</sup>

### 13.2.3. Axial arthropathy

Asymptomatic sacroiliitis is common, with up to 50% of colitis patients having abnormal radiography.<sup>279</sup> Symptomatic sacroiliitis is characterised by pain in the buttocks after rest, which then improves with movement. The clinical sign of discomfort in the sacroiliac joints during bilateral pressure on the pelvic brim is indicative. The principal symptom of ankylosing spondylitis is persistent low back pain, usually beginning before the age of 30. Clinical examination reveals loss of the lumbar lordosis and limited spinal flexion. Conventional radiographs of the back are usually normal in the early stages of disease. Spinal CT scans and radionuclide bone scans are more sensitive than plain radiographs, but the gold standard is now magnetic resonance imaging (MRI).<sup>280,281</sup> There is however an impression that minor abnormalities of little or no clinical consequence may be seen on MRI; this remains to be determined by longer-term follow-up. In advanced cases there may be squaring of the vertebral bodies, marginal syndesmophytes and bony proliferation, with ankylosis producing the classical “bamboo spine”. HLA B-27 associations is found in a majority (up to 75%) of patients with axial arthritis, but is less common than in patients with ankylosing spondylitis not associated with IBD. It is unrelated to sacroiliitis and HLA typing has no role in the management of individual patient.<sup>282,283</sup>

### 13.2.4. Therapy of arthropathies

#### ECCO Statement 13B

Treatment of arthritis and arthropathy associated with UC is based almost entirely on extrapolation from that for other forms of arthritis. There is some support for use of sulfasalazine, simple analgesics, non-steroidal anti-inflammatory agents, local steroid injections, and physiotherapy [EL4, RG D]. In Type I peripheral arthritis the emphasis should be on that of the underlying colitis [EL2c, RG C]. In axial arthritis the arguments in favour of intensive physiotherapy [EL2a, RG B], sulfasalazine [EL2a, RG C], methotrexate [EL3b, RG C], and infliximab [EL2a, RG C], are somewhat stronger

Treatment of arthritis and arthropathy associated with IBD is largely empirical. This includes the use of simple analgesics, sulfasalazine, local steroid injections and physiotherapy, but whether or not to use non-steroidal anti-

inflammatory agents is a continuing dilemma, even though short term use appears not to exacerbate colitis.<sup>284</sup>

For Type I peripheral arthritis the emphasis should be on the treatment of active disease, including steroids, immunomodulation, and anti-TNF therapy as appropriate. Resolution of the arthropathy can be expected. The joint-specific drug of first choice for all forms of IBD-related arthritis appears to be sulfasalazine, but convincing evidence to support this is lacking. Nevertheless, it was favoured by the greatest minority of panel members (41%). Symptomatic relief may be obtained from simple analgesics, rest and physiotherapy.<sup>279,284,285,286</sup> Although there is concern that non-steroidal anti-inflammatory agents (conventional and COX II inhibitors) may aggravate the underlying colitis,<sup>287,288</sup> they have been used by many gastroenterologists to good effect with limited risk of exacerbating colitis. A previous history of flare related to NSAID intake seems to be the best indicator of individual risk. A randomised study of the safety of celecoxib in colitis<sup>283</sup> indicated that short-term use (<2 weeks) did not exacerbate colitis. Local steroid injection into the worst-affected joints often provides rapid, but temporary relief. Type II arthritis generally resolves with effective treatment of the colitis.<sup>289</sup>

Treatment of axial arthritis should include intensive physiotherapy, together with disease modifying drugs such as sulfasalazine, and methotrexate.<sup>279,285,289</sup> The safety and efficacy of infliximab in ankylosing spondylitis is established, but is best reserved for intractable or severely debilitating symptoms.<sup>290,291</sup> This is because of the 15% prevalence of immunogenicity and the small, but definable risk of notable adverse events such as sepsis, tuberculosis, or demyelination.

### 13.3. Cutaneous manifestations

#### ECCO Statement 13C

Diagnosis of the cutaneous manifestations of UC is made on clinical grounds, based on their characteristic features and (to some extent) the exclusion of other specific skin disorders; biopsy is rarely appropriate or necessary [EL3b, RG C]

#### 13.3.1. Erythema nodosum

Erythema nodosum is usually readily recognised. It is characterised by raised, tender, red or violet subcutaneous nodules of 1 to 5 cm in diameter. It commonly affects the extensor surfaces of the extremities, particularly the anterior tibial area, and usually occurs at times of activity of the colitis. A firm clinical diagnosis can normally be made, and biopsy is not normally appropriate. If performed, the histology reveals a non-specific focal panniculitis.<sup>292,293</sup>

Because erythema nodosum is closely related to disease activity, despite a genetic link,<sup>294</sup> treatment is based on that of the underlying colitis. Systemic steroids are usually required (76% Consensus view). In resistant cases or when there are frequent relapses, immunomodulation with azathioprine and/or infliximab may be added, but it is exceptional to need such measures just because of erythema nodosum. Oral potassium iodide has been used successfully in refractory cases.<sup>295</sup>

### 13.3.2. Pyoderma gangrenosum (PG)

Lesions are often preceded by trauma at the site (which may have been many years earlier) through a phenomenon known as pathergy. PG can occur anywhere on the body, including the genitalia, but the commonest sites are the shins and adjacent to stomas. Initially they take the form of single or multiple erythematous papules or pustules, but subsequent necrosis of the dermis leads to the development of deep excavating ulcerations that contain purulent material that is sterile on culture unless secondary infection has occurred.

Treatment of pyoderma gangrenosum has relied on topical and systemic steroids. Steroids were considered the most effective treatment for pyoderma gangrenosum (54% Consensus view), with intravenous ciclosporin or tacrolimus reserved for refractory cases.<sup>296–298</sup> There are, however, no reliable trials to support the use of high dose steroids or calcineurin inhibitors and these drugs have appreciable potential side-effects. Infliximab has changed the management of PG. In the first controlled trial in pyoderma (which also included patients without IBD) infliximab 5 mg/kg or placebo was given at week 0.<sup>299</sup> At week 2 (the primary end point), significantly more patients in the infliximab group had improved (46% (6/13)) compared with the placebo group (6% (1/17),  $p=0.025$ ). Overall, 29 patients received infliximab with 69% (20/29) demonstrating a beneficial clinical response. Remission at week 6 was 21% (6/29). There was no response in 31% (9/29) of patients. Infliximab is still reserved for more troublesome cases, but is highly effective.

### 13.3.3. Sweet's syndrome

Sweet's syndrome is characterised by tender, red inflammatory nodules or papules, usually affecting the upper limbs, face or neck. It has only been recognised as an extraintestinal manifestation of IBD relatively recently.<sup>300,301</sup> It is part of the group of acute neutrophilic dermatoses that includes pyoderma gangrenosum, but can be distinguished by its appearance, distribution and histological features. There is a strong predilection for women (87%), patients with colonic disease (100%) and those with other extraintestinal features (77%). The rash is associated with active disease in 67–80%, but may precede the onset of intestinal symptoms in 21% and has been reported 3 months after proctocolectomy for ulcerative colitis.

## 13.4. Ocular manifestations

Uveitis and episcleritis are probably the most common extraintestinal manifestations of IBD.<sup>273,302</sup>

#### ECCO Statement 13D

A confident diagnosis of simple episcleritis may not require specific treatment, but if necessary will usually respond to topical steroids [EL4, RG D]. When diagnosis is uncertain referral to an ophthalmologist for expert opinion and slit-lamp examination is recommended [EL4, RG D]. Uveitis is treated with steroids, and it may be necessary to use both topical and systemic routes [EL3b, RG C]. Immunomodulatory therapy has been thought helpful in resistant cases [EL4, RG D]

### 13.4.1. Episcleritis

Episcleritis may be painless, presenting simply with hyperaemic sclera and conjunctiva, but itching and burning sensations may also occur.<sup>303</sup> Diagnosis of simple episcleritis depends on the exclusion of the more sinister features of uveitis. When this is not possible referral to an ophthalmologist for an expert opinion and slit-lamp examination is essential. Episcleritis usually does not require specific treatment other than for underlying disease activity. It will respond to topical steroids if symptoms are troublesome – but take care that infection (including herpetic), ulceration, and uveitis are not overlooked.

### 13.4.2. Uveitis

Uveitis is less common, but has potentially severe consequences. When related to ulcerative colitis it is frequently bilateral, insidious in onset and long-lasting.<sup>304</sup> Patients complain of eye pain, blurred vision, photophobia and headaches. Potential progression to loss of vision should prompt urgent referral to an ophthalmologist. Slit-lamp examination will confirm the diagnosis and differentiates between anterior and posterior uveitis. Uveitis is treated with steroids, and it may be necessary to use both topical and systemic routes. Infliximab is rapidly effective,<sup>304</sup> but treatment should be guided by specialists.

### 13.4.3. Cataracts

Chronic corticosteroid use for treatment of UC is associated with numerous complications and may result in posterior subcapsular cataracts develop in a significant proportion (25%) of patients receiving 15 mg or more of prednisone for 1 year.<sup>305</sup> Although steroids do not prevent relapse and have no place in the long-term management of UC, any patient on long-term steroids should undergo routine (probably annual) slit lamp examination.

## 13.5. Hepatobiliary disease

Hepatobiliary disease is relatively common in IBD and magnetic resonance cholangiography (MRC) indicates that it may be more prevalent than currently estimated in ulcerative colitis.<sup>306</sup> Primary sclerosing cholangitis (PSC) constitutes the most important condition relatively specific to the underlying IBD. Other conditions associated with IBD more commonly than in the general population include pericholangitis, steatosis, chronic hepatitis, cirrhosis, and gallstone formation. Hepatotoxicity from some drugs used for colitis should always be considered, although usually presents within 3 weeks of starting medication and not at later stages.

The finding of abnormal liver function tests, rather than symptoms or signs of liver disease, is the most common presentation. Diagnosis of hepatobiliary disorders then follows the standard investigatory pathways for abnormal liver function tests, with ultrasound scanning, serology to identify specific auto-immune or infective causes, and liver biopsy. Predominantly cholestasis or the biliary-type pain will prompt ultrasonographic assessment, which may reveal gall stones, steatosis, be consistent with cirrhosis, or (less often) show an abnormal duct pattern suggestive of PSC.

**ECCO Statement 13E**

PSC appears to respond to ursodeoxycholic acid, which improves abnormal liver function tests [EL1b, RG B] and may, at 20 mg/kg, improve liver histology and prognosis [EL2a, RG C]. It is possible that ursodeoxycholic acid also reduces the risk of colonic cancer in PSC patients [EL2a, RG C]. ERCP may be used to treat dominant strictures by dilatation and/or stenting [EL4, RG C]. Advanced liver disease may necessitate transplantation [EL2a, RG B]

**13.5.1. Primary sclerosing cholangitis**

For patients with cholestasis the probability of PSC is appreciably increased if the ultrasound scan is normal, if drug side-effects are thought unlikely, and if serological tests for primary liver disease are negative. Magnetic resonance cholangiography (MRC) is now established as the first-line diagnostic test for PSC.<sup>307</sup> The characteristic pattern shows irregular bile ducts, with zones of both narrowing and dilatation. If MRC is normal and PSC still suspected (such as otherwise unexplained cholestasis in a patient with IBD), then it is safer and probably more effective to do a liver biopsy rather than diagnostic ERCP, since this will detect predominant small duct disease. PSC substantially increases the risk of both cholangiocarcinoma and colorectal carcinoma (Section 9.1.2, 9.5).

PSC appears to respond to ursodeoxycholic acid (ursodiol), which improves abnormal liver function tests<sup>308</sup> and may, at 20 mg/kg, possibly improve prognosis. It is possible that it also reduces the risk of colonic cancer in these patients<sup>118</sup> (Section 9.5). Tacrolimus has yielded a rapid decrease in liver enzymes, but no histological improvement.<sup>309</sup> ERCP may be used to treat dominant strictures by dilatation and/or stenting. Advanced liver disease may necessitate transplantation, but recurrence of PSC in the transplanted liver occurs in approximately 20% of patients.<sup>308,310</sup> Specialist advice is appropriate when managing a patient with PSC and IBD. Because of the higher risk of colorectal cancer, it is generally considered appropriate to perform annual screening colonoscopy from the time of diagnosis.

**13.6. Metabolic bone disease****ECCO Statement 13E**

Diagnosis of osteoporosis in adults is best made from a *T* score of less than  $-2.5$  on radiographic bone densitometry [EL1a, RG A], all other diagnostic methods having current limitations [EL2b, RG B]. The presence of osteoporosis identifies patients at above average risk for fracture and who should receive treatment [EL2b, RG B]

**ECCO Statement 13F**

Osteopenia may be a prognostic marker for future osteoporosis, but presents little direct risk [EL2b, RG C]. However if the *T* score is less than  $-1.5$ , treatment with calcium, vitamin D and a bisphosphonate should be considered [EL4, RG C]. Pre-existing history of fracture is of substantial adverse prognostic significance and such patients should be treated for osteoporosis even if the *T* score is normal [EL4, RG C]

**13.6.1. Diagnosis and fracture risk**

Osteoporosis and osteopenia are common in patients with IBD (20–50%), but the actual number of fractures in IBD is only slightly increased to the general population.<sup>311,312</sup> In a study using the general practice research database, the relative risk of hip fracture was 1.62 (95% CI 1.24–2.11) for all IBD, 1.49 (1.04–2.15) for ulcerative colitis and 2.08 (1.36–3.18) for Crohn's disease.<sup>312</sup> Contributing factors include age, steroid treatment, smoking, low physical activity (including that from hospitalisation), inflammatory cytokines, and probably also resection with pouch formation.

Diagnosis is conventionally based on bone densitometry (DEXA scanning), osteoporosis being defined as a *T* score of less than  $-2.5$ . Ultrasound has been suggested as method of screening, but is not yet reliable. The presence of osteoporosis increases the risk of fracture of long bones and of the spine, although probably a great deal less in young patients than was once thought. It is conventional to use a radiological diagnosis of osteoporosis as an indication for specific therapy.

Osteopenia (*T* score less than  $-1.0$ ) is thought by some to be an important risk factor for fracture in its own right, but this is increasingly questioned.<sup>313</sup> It is, however, probable that it is a marker of increased risk of later osteoporosis even if the risk is not absolute. Therapeutic intervention is probably not justified on present knowledge, but continued surveillance for bone loss is appropriate. It is important to put risks into perspective when discussing with patients.

The risks of osteoporosis (and the potential risks from osteopenia) should be explained. The recommended dietary calcium intake should be 1000–1500 mg/day, which often means supplementation even in patients not taking corticosteroids. It should be noted that recommendations for the treatment of osteoporosis apply only to adults over the age of 25 years, and that evidence for treating osteopenia is circumstantial. The diagnosis of osteoporosis in children and long-term consequences of treatment with bisphosphonates are unknown.

**13.6.2. Management****ECCO Statement 13G**

Weight-bearing exercise [EL2b, RG B], stopping smoking [EL3b, RG C], avoiding alcohol excess [EL4, RG D], and maintaining adequate dietary calcium ( $>1$  g/day) [EL2b, RG B] are beneficial. In post-menopausal women with osteoporosis, regular use of bisphosphonates, calcitonin and its derivatives, and raloxifene reduce or prevent further bone loss [EL2b, RG C]. Data in males with osteoporosis are less secure but bisphosphonates are probably of value [EL3b, RG C]. Newer data also support the use of strontium salts [EL2a, RG B]

The risks of osteoporosis (and the potential risks from osteopenia) should be explained. The treatment of osteoporosis is based on studies that are not specific to IBD.<sup>314</sup> Weight-bearing, isometric exercise, stopping smoking, avoiding alcohol excess and maintaining adequate dietary calcium ( $>1$  g/day) are beneficial, but such advice is often overlooked. Hormone replacement treatment is no longer generally advised in post-menopausal women with osteoporosis, because studies have demonstrated a slightly increased risk of breast cancer and of

cardiovascular events.<sup>315</sup> Regular use of bisphosphonates, calcitonin and its derivatives, and raloxifene (a selective oestrogen receptor modulator) may reduce or prevent further bone loss. Data in males with osteoporosis are few, but bisphosphonates are probably of value and an important practice point is that testosterone should be measured. Those with low testosterone may benefit from supplementation. Routine administration of vitamin D is not warranted. Patients on corticosteroids for short periods do not merit routine use of bone protection with bisphosphonates, assuming a normal calcium intake and all other risk factors being equal.<sup>315</sup>

### 13.7. Other systems

Other systems are found to be abnormal in UC more often than would be expected by chance and these associations may therefore be considered to be extra-intestinal manifestations. Examples include respiratory complaints (especially asthma), cardiac and pericarditic conditions, nephrological disease (both nephritis and amyloidosis), neurological conditions (especially multiple sclerosis) and urinary tract stones.<sup>274,302</sup> Their diagnosis and management is not considered in further detail, because the routes to diagnosis are no different from those in general medical practice and because their management is fundamentally independent of that of the colitis. The issue of interstitial nephritis associated with 5-ASA therapy<sup>316</sup> is considered in the section on colitis therapy (Section 5.4.1, preceding paper same issue.)<sup>289</sup> Anaemia and ulcerative colitis deserves greater proactive management by gastroenterologists than it generally receives, because it is associated with substantial impairment of the quality of life. Reasons for not treating anaemia effectively often dwell on intolerance to oral iron therapy and difficulty in delivering or risks associated with parenteral iron, but this is no longer tenable and expectations of both patients and physicians should be raised.<sup>276</sup>

### 13.8. Organisation of services for EIMs associated with ulcerative colitis

#### ECCO Statement 13 G

Organisation of services to facilitate expert management of extra-intestinal manifestation may include combined or parallel specialist clinics conducted with clinicians from the other relevant disciplines [EL4, RG D]

The more common extra-intestinal manifestations affecting joints and skin may be profitably managed by a close working relationship between the gastroenterologist and rheumatologist or dermatologist respectively. It is easier to ensure that inter-disciplinary knowledge is used to best advantage for the patient by the existence of periodic clinics for rheumatology, dermatology and other specialties held in parallel, and in some cases by joint consultations. Awareness of atypical presentations and of new exploratory therapies is therefore enhanced.

## 14. Complementary and alternative medicines

### 14.1. Introduction

The use of complementary and alternative medicine among UC patients is common, and physicians are frequently

confronted with questions about their use. Reasons for using such therapies are worries about conventional treatment, including perceived lack of effectiveness and fear about side-effects, in addition to subjective benefit from complementary or alternative therapies. However, evidence for the efficacy and safety of CAMs is often lacking, because there are very few controlled trials that assessed these therapies in UC and even these are underpowered for what they aim to establish. Consequently, because of the lack of power and other methodological problems in the reported studies, it is difficult for physicians to inform their patients adequately. Nevertheless, complementary and alternative treatments warrant further evaluation from public interest alone. Although complementary medicine appears to be generally safe and non-toxic, this cannot be assumed and potential side-effects should be considered for each substance, particularly when microorganisms are used in conjunction with conventional immunomodulators.

### 14.2. Definitions

#### ECCO Statement 13A

Alternative medicines for ulcerative colitis (UC) exclude the possibility of using conventional therapy at the same time [EL5, RG D]. Complementary medicines for UC allow concomitant conventional therapy [EL5, RG D]

Complementary and alternative medicines represent a diverse group of medical and non-medical products and therapeutic approaches that are not presently considered part of conventional therapy. Products that have established efficacy in UC, such as specific probiotics (*E. coli* Nissle 1917, for example), are not considered complementary or alternative medicines and are described elsewhere (Section 6.2.4, preceding paper same issue). On the other, hand remedies from different, often non-Western, cultures are included in this group of therapies, as well as those that are unproven. An important distinction between alternative and complementary medicine is its relation to conventional therapy. Alternative medicine explicitly excludes concomitant conventional therapy, but complementary medicine allows the complementary approach in conjunction with conventional therapy. It is helpful if patients are aware of this distinction, not least because alternative medicine for a serious, potentially life-threatening condition such as acute severe colitis would be dangerous.

### 14.3. Use of CAM

#### ECCO Statement 13B

Alternative medicine for UC as defined above is strongly discouraged [EL5, RG D]

Since alternative medicine by definition does not allow conventional therapy, even when necessary, this type of UC therapy can lead to severe complications from the underlying condition. In contrast, complementary medicine is usually safe and is possible if patients want to use it. From a practical point of view, if patients discuss complementary therapy in the context of conventional medical consultation, it is usually an indicator

that the patient or their family want to know more about their condition, the conventional medicine that is being prescribed, and the therapeutic strategy. It should alert practitioners to unmet need, if only for more detailed explanation.

#### ECCO Statement 13C

UC patients should be asked about the use of alternative and complementary medicines [EL5, RG D]

Complementary and alternative medicines are commonly used by UC patients.<sup>317–321</sup> Although the use of complementary medicine is considered largely safe, there are published case reports on systemic fungal infection in immunocompromised patients.<sup>321</sup> In addition, herbal medicine such as St John's Wort, can interact with immunosuppressive agents and need to be checked for potential interactions.<sup>322,323</sup> It is therefore appropriate to enquire about the use of alternative and complementary medicine.

#### ECCO Statement 13D

There is insufficient evidence for the use of *Trichuris suis* ova, *Saccharomyces boulardii*, or *Bifidobacteria* in the treatment of UC [EL5, RG D]

Although some probiotics and one helminth have been investigated in clinical studies, these publications are considered of insufficient power to take a view on whether to recommend their use. Their design was single centre and sample size too small.<sup>324–329</sup>

#### ECCO Statement 13E

There is insufficient evidence for the use of acupuncture, *Boswellia serrata* gum, germinated barley, aloe vera gel and other herbal medicines in the treatment of UC [EL5, RG D]

Other complementary medicines have been studied in small studies or in countries where randomised, double-blind, placebo-controlled trials are not the practice norm for judging the merits of therapy. Because of sample size, study design, concomitant therapies and questionable transferability, the following agents cannot currently be recommended for treating UC, either active disease or as maintenance: acupuncture,<sup>330–332</sup> *Boswellia serrata* gum,<sup>333</sup> prebiotic germinated barley foodstuff,<sup>334–336</sup> aloe vera gel<sup>337</sup> and other herbal medicines.<sup>338</sup> A report on curcumin maintenance therapy (2 g daily, added to aminosalicylates for 6 months) showed a signal for benefit in a double-blind, placebo-controlled trial of 89 patients.<sup>339</sup> This both needs confirmation and illustrates the need to explore complementary medicines subject to the same rigorous proof of benefit as conventional therapy.<sup>340</sup>

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