



SPECIAL ARTICLE

# Second European evidence-based consensus on the diagnosis and management of ulcerative colitis Part 3: Special situations

Gert Van Assche<sup>\*,1,2</sup>, Axel Dignass<sup>\*\*2</sup>, Bernd Bokemeyer<sup>1</sup>, Silvio Danese<sup>1</sup>, Paolo Gionchetti<sup>1</sup>, Gabriele Moser<sup>1</sup>, Laurent Beaugerie<sup>1</sup>, Fernando Gomollón<sup>1</sup>, Winfried Häuser<sup>1</sup>, Klaus Herrlinger<sup>1</sup>, Bas Oldenburg<sup>1</sup>, Julian Panes<sup>1</sup>, Francisco Portela<sup>1</sup>, Gerhard Rogler<sup>1</sup>, Jürgen Stein<sup>1</sup>, Herbert Tilg<sup>1</sup>, Simon Travis<sup>1</sup>, James O. Lindsay<sup>1</sup>

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\* Correspondence to: G. Van Assche, Division of Gastroenterology, Department of Medicine, Mt. Sinai Hospital and University Health Network, University of Toronto and University of Leuven, 600 University Avenue, Toronto, ON, Canada M5G 1X5.

\*\* Correspondence to: A. Dignass, Department of Medicine 1, Agaplesion Markus Hospital, Wilhelm-Epstein-Str. 4, D-60431 Frankfurt/Main, Germany.

E-mail addresses: [gvanassche@mtsina.on.ca](mailto:gvanassche@mtsina.on.ca) (G. Van Assche), [axel.dignass@fdk.info](mailto:axel.dignass@fdk.info) (A. Dignass).

<sup>1</sup> On behalf of ECCO.

<sup>2</sup> G.V.A. and A.D. acted as convenors of the consensus and contributed equally to this paper.

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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 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 pouchitis more commonly develops within the first years after IPAA or whether the risk continues to increase with longer follow up remains undefined.

#### Statement 8A

The diagnosis of pouchitis requires the presence of symptoms, together with characteristic endoscopic and histological abnormalities [EL3a, RG B]. Extensive UC, extraintestinal manifestations (i.e. PSC), being a non-smoker, p-ANCA positive serology and NSAID use are possible risk factors for pouchitis [EL3b, RG D]

#### 8.1.1. Symptoms

After proctocolectomy with IPAA, median stool frequency is 4 to 8 bowel movements,<sup>1-4,13,14</sup> with about 700 mL of semiformed/liquid stool per day,<sup>2,13,14</sup> compared to a volume of 200 mL/day in healthy people. Symptoms related to pouchitis include increased stool frequency and liquidity, abdominal cramping, urgency, tenesmus and pelvic discomfort.<sup>2,15</sup> Rectal bleeding, fever, or extraintestinal manifestations may occur. Rectal bleeding is more often related to inflammation of the rectal cuff ("cuffitis," Section 1.4),<sup>16</sup> than to pouchitis. 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> among other conditions. This is why the diagnosis depends on endoscopic and histological findings 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>15,21</sup> Patients with an ileoanal pouch occasionally have a stricture at the

pouch-anal anastomosis, so a gastroscope rather than a colonoscope is preferred for pouchoscopy. Progression into the afferent ileal limb should always be attempted. Endoscopic findings compatible with pouchitis include diffuse erythema, which may be patchy, unlike that observed in UC. Characteristic endoscopic findings also 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.<sup>18,22,23</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>22,23</sup> There may be discrepancy between endoscopic and histologic findings in pouchitis, possibly related to sampling error.<sup>24,25</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 complete disappearance of the villi, leading to villous atrophy ("colonic metaplasia").<sup>23-25</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/or other triggers of inflammation in UC are involved.<sup>26,27</sup> Pouchitis tends to occur only after colonic metaplasia has developed in the pouch, although a causal association is unproven.

#### 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>28-30</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>31</sup> The possibility of non-specific ileitis caused by NSAIDs should be considered.<sup>32</sup>

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

The aetiology of pouchitis remains unclear. Risk factors, genetic associations, and serological markers of pouchitis suggest that a close interaction between the host immune response and the pouch microbiota plays a relevant role in the aetiology of this idiopathic inflammatory condition.<sup>33</sup> Reported risk factors for pouchitis include extensive UC,<sup>1,34</sup> backwash ileitis,<sup>34</sup> extraintestinal manifestations (especially primary sclerosing cholangitis),<sup>5,19,35</sup> being a *non-smoker*<sup>36</sup> and regular use of NSAIDs.<sup>32,37</sup> Interleukin-1 receptor antagonist gene polymorphisms<sup>38</sup> and the presence of perinuclear neutrophil cytoplasmic antibodies<sup>39</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>40</sup> Two hundred and forty 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 when the indication for IPAA was dysplasia (OR 3.89; 95% CI 1.69–8.98), when the patient had never smoked (OR 5.09; 95% CI 1.01–25.69), 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 a diagnosis of Crohn's disease in the pouch was greatly increased by being a current smoker (OR 4.77; 95% CI, 1.39–16.25), and modestly increased with 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>40</sup> Similar to irritable bowel syndrome, a visceral hypersensitivity has been described in these patients.<sup>41</sup> The same group has recently shown that various perioperative factors may predict pouchitis. On multivariate analysis, pulmonary comorbidity, disease proximal to the splenic flexure, extraintestinal manifestations, and S-pouch reconstruction were associated with pouchitis.<sup>42</sup> These risk factors should not preclude proctocolectomy if surgery is appropriate, but should be included pre-operative discussions with the patient and family. 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. These discussions are part of appropriate management of expectations and known predictive factors for pouchitis or irritable pouch should not be considered as formal contraindications for pouch 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>15,43</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> From various perspectives pouchitis may also be classified into: 1) idiopathic versus secondary, 2) in remission versus active, 3) infrequent (<3 episodes per year) versus relapsing (>3 episodes per year). Pouchitis may also be classified based on the response to antibiotic therapy: 1) antibiotic-responsive, 2) antibiotic-dependent (need for continuous antibiotic treatment to maintain remission), 3) antibiotic-refractory.<sup>44</sup>

### 8.2.2. Scoring of pouchitis

The Pouchitis Disease Activity Index (PDAI) has been developed to standardise diagnostic criteria and assess the severity of pouchitis.<sup>15,43,45</sup> The PDAI is a composite score that evaluates symptoms, endoscopy and histology. Each component of the score has a maximum of 6 points. Patients with a total PDAI score  $\geq 7$  are classified as having pouchitis although a patient should exhibit both clinical symptoms and endoscopic or histological evidence of pouchitis. 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 the Moskowitz index<sup>22</sup> and an index from Heidelberg. Comparisons with the PDAI<sup>46,47</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% patients.<sup>3,15,41</sup> Patients with recurrent pouchitis can broadly be grouped into three categories: infrequent episodes (<1/year), a relapsing course (1–3 episodes/year) or a continuous course. Pouchitis may further be termed treatment responsive or refractory, based on response to antibiotic mono-therapy<sup>7,9</sup> (see Section 1.3.2). 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>7,28,43</sup> The 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

#### 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, RG D]

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 resulting in a rapid response. The odds ratio of inducing response using oral metronidazole compared with placebo in active chronic pouchitis is 26.67 (95% CI 2.31–308.01, NNT=2).<sup>48</sup> However, randomised trials of both metronidazole and ciprofloxacin are small.<sup>3,49</sup> The two have been compared in another small randomised trial<sup>50</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 benefit with 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). The treatment and prevention of pouchitis has been systematically reviewed in 2010 by a Cochrane analysis. For the treatment of acute pouchitis (4 RCTS, 5 agents) ciprofloxacin was more effective at inducing remission than metronidazole. Neither rifaximin nor *Lactobacillus plantarum* GG were more effective than placebo, while budesonide enemas and metronidazole were equally effective for inducing remission. In a non-randomised, non-controlled, open-label trial, a highly concentrated probiotic preparation (VSL#3) was shown to be effective in the treatment of mildly active pouchitis.<sup>51</sup>

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

#### Statement 8D

In chronic pouchitis a combination of two antibiotics is effective [EL1b, RG B]. Oral budesonide is an alternative [EL2b, RG B]. Infliximab is effective for the treatment of chronic refractory pouchitis [EL4, RG C]

For patients who have persistent symptoms, alternative diagnoses should be considered, including undiagnosed Crohn's disease, pouch-anal or ileal-pouch stricture, infection 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>45</sup>

Patients with chronic, refractory pouchitis do not respond to conventional therapy and often have ongoing symptoms. This is a common cause of pouch failure. Combination antibiotic therapy or oral budesonide may be effective. Sixteen 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>52</sup> A historic cohort of ten consecutive patients with chronic refractory pouchitis treated with high dose oral and topical mesalazine daily was used as a comparator. These treatment-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 refractory 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>53</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>54</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>55</sup> Thirty-six 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>56</sup> Oral budesonide also appears to have no impact on liver function tests in pouchitis patients with PSC, while improving significantly the pouch and afferent limb inflammation.<sup>57</sup> The cumulative data (derived mainly from underpowered trials) suggest that, if ciprofloxacin does not work, it should be tried in combination with an imidazole antibiotic or rifaximin, with an alternative being oral budesonide.

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

A variety of approaches has been assessed in open label and small controlled trials. Budesonide enemas were as effective as metronidazole for acute pouchitis in a randomised controlled trial.<sup>58</sup> Ciclosporin enemas were successful for chronic pouchitis in a pilot study<sup>59</sup> and oral azathioprine may help if patients relapse become budesonide-dependent. Uncontrolled studies of short-chain fatty acid enemas and suppositories.<sup>60–62</sup> Of more interest, infliximab has been tried in patients with chronic, refractory pouchitis.<sup>63</sup> A series of 28 patients with an IPAA who had developed refractory pouchitis were treated with infliximab. Patients had either pouchitis/pre-pouch ileitis ( $n=25$ ) and/or pouch fistula ( $n=7$ ) (patients with evidence of known Crohn's disease were excluded). 82% of patients received concomitant immunomodulator therapy. After 10 weeks of therapy 88% of treated patients showed a clinical response (14 partial, 8 complete) and 6/7 patients with a fistula improved (3 partial, 3 complete). PDAI decreased from 9.0 to 4.5 points. In

addition, clinical responses after a median follow-up of 20 months were observed in 56% patients. Five patients needed permanent ileostomy.<sup>63</sup> The effect of infliximab in ten patients with chronic refractory pouchitis complicated by ileitis has also been described<sup>64</sup>; 9/10 patients achieved clinical remission and 8/10 demonstrated complete recovery of endoscopic lesions which was maintained for at least 6 months. More recently, in a multicentre Spanish retrospective study, 33 patients with chronic refractory pouchitis were treated with infliximab. 21%, 33% and 27% achieved complete response at week 8, 26 and 52.<sup>65</sup> Although infliximab might be an effective long-term therapy for pouchitis, clinical data are still few and prospective, multicentre, randomised controlled trials are needed. A possible alternative for patients with chronic refractory pouchitis previously treated with infliximab may be adalimumab; 50% of patients avoided a permanent ileostomy after 1 year of treatment with adalimumab.<sup>66</sup>

Finally, benefit has been reported from alicaforsen enemas (an inhibitor of intercellular adhesion molecule (ICAM)-1) in an open-label trial. Twelve patients with chronic refractory pouchitis were treated with 240 mg enemas and 7/12 (58%) were in remission after 6 weeks.<sup>67</sup>

### 8.3.4. Maintenance of remission: probiotics

#### Statement 8E

Probiotic therapy with 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]

Once remission has been obtained in chronic pouchitis, treatment with the concentrated probiotic mixture VSL#3 helps 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 1 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>68</sup> All 20 patients who received placebo relapsed, while 17/20 patients (85%) treated with VSL#3 remained in clinical and endoscopic remission at the end of the study. Interestingly, all 17 patients relapsed within 4 months of stopping VSL#3. 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 1 year were 85% in the VSL#3 group and 6% in the placebo group ( $p < 0.001$ ).<sup>69</sup> In the Cochrane systematic review VSL#3 was more effective than placebo in maintaining remission of chronic pouchitis in patients who achieved remission with antibiotics.<sup>51</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 of 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>70</sup> A Cochrane systematic review reports that VSL#3 was more effective than placebo for the prevention of pouchitis.<sup>51</sup> The mechanism of action of probiotic therapy remains elusive.<sup>71</sup> Patients who develop pouchitis have low bacterial and high fungal diversity in the mucosa-associated pouch microbiota. Bacterial diversity was increased and fungal diversity was reduced in patients in whom remission was maintained using VSL#3 ( $p = 0.001$ ). VSL#3 increased the total number of bacterial cells assessed by real time PCR ( $p = 0.002$ ) 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 by probiotic therapy. The diversity of the fungal flora was repressed. Restoration of the integrity of a "protective" intestinal mucosa related microbiota could therefore be one mechanism by which probiotic bacteria work.

### 8.4. Cuffitis

#### Statement 8F

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 can cause pouch dysfunction with symptoms that mimic pouchitis or irritable pouch syndrome (IPS) especially after double-stapled IPAA (see Section 7). Unlike IPS (which may coexist) bleeding is a characteristic feature of cuffitis. Endoscopy 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).<sup>72</sup> In an open-label trial, 14 consecutive patients with cuffitis treated with mesalazine suppositories 500 mg twice daily experienced a reduction in the total Cuffitis Activity Index (derived from the PDAI) from  $11.9 \pm 3.17$  to  $6.21 \pm 3.19$  ( $p < 0.001$ ).<sup>16</sup> In addition the symptom subscore reduced 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 from  $4.93 \pm 1.77$  to  $3.57 \pm 1.39$ . 92% of patients with bloody bowel movements and 70% with arthralgia (a characteristic clinical feature of cuffitis (Section 1.1.4)) improved on therapy. No systemic or topical adverse effects were reported.

## 9. Surveillance for colorectal cancer in UC

### 9.1. Risk of colorectal cancer in UC

#### Statement 9A

Patients with longstanding ulcerative colitis have an increased risk of colorectal cancer compared to the general population [EL 1b, RG B]

Although it is generally accepted that longstanding ulcerative colitis is associated with an increased risk of colorectal carcinoma (CRC), the reported risk estimates vary widely. In 2001, Eaden published a frequently cited meta-analysis of 116 studies dating from 1935 to 1999.<sup>73</sup> Based on 19 of these 116 studies, cumulative risks up to 18% at 30 years of disease duration were found. Older studies, which often originate from referral centres, even report cumulative risks up to 43%,<sup>74</sup> while risks in newer, population-based studies seem to be hardly increased as compared to the general population.<sup>75–77</sup> These differences have been attributed to differences in study design, study population and patient selection. The risks of CRC seem to decline over time as well, as highlighted in a study from St. Marks.<sup>78</sup> This might reflect an increased implementation of surveillance strategies, introduction of drugs that control inflammation more effectively, or a changing approach to maintenance therapy or colectomy. Hence, it seems that patients with longstanding ulcerative colitis carry an increased risk of developing CRC, but this risk is probably not as high as previously perceived.

#### Statement 9B

The risk of colorectal cancer in ulcerative colitis is associated with disease duration and extent [EL 1b, RG B]

In the Eaden meta-analysis, cumulative CRC risks of 2% at 10 years, 8% at 20 years and 18% at 30 years disease duration were reported. Although it has been stated that CRC is rarely encountered when disease duration is less than 8 years, a significant number of tumours might develop within this time window,<sup>76,79</sup> especially in patients who are older at colitis onset. Whether these early CRC cases are truly colitis-associated or sporadic carcinomas cannot be determined from these studies. The role of disease extent with regard to the CRC risk is undisputed. Patients with pancolitis or colitis extending proximal to the splenic flexure carry the highest risks, and patients with a left sided colitis having an intermediate risk profile. CRC risk is not increased in patients with UC limited to the rectum.<sup>73</sup> Of note, histological extent, even without endoscopically visible abnormalities, may be an important determinant of the cancer risk as well.<sup>80</sup>

#### Statement 9C

Concomitant Primary Sclerosing Cholangitis (PSC), post-inflammatory polyps, a family history of CRC and more severe or persistent inflammatory activity confer an additional risk for CRC in ulcerative colitis patients [EL 1b, RG B]

The wide variation of risk estimates reported in literature may be attributed to differences in additional risk factors in the patient cohorts studied. The most consistent risk factors reported are primary sclerosing cholangitis (PSC) with a CRC risk up to 31%<sup>81–83</sup> and histological or clinical disease activity.<sup>84–86</sup> Post-inflammatory polyps may be markers of previous inflammatory severity and have also been found to be strong risk factors.<sup>75,84,87</sup> However it is possible that this increased risk relates to missed dysplastic lesions mistakenly diagnosed as post-inflammatory polyps. Early onset of disease before the age of 20–25 years may also contribute to an increased risk, although it cannot be distinguished from the published data whether this is a truly independent risk factor or solely explained by disease duration.<sup>76,77,88</sup> A family history of CRC is associated with an increased risk, although not consistently so across the studies.<sup>82,89</sup>

### 9.2. Surveillance issues

#### 9.2.1. Screening and surveillance

Since dysplastic change in colonic mucosa is associated with an increased risk of colorectal cancer (CRC) in ulcerative colitis (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 involves not only performing repeated colonoscopies, but includes reviewing the patient's symptoms, medications and laboratory test results, as well as updating personal and family 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.

#### 9.2.2. Effectiveness

#### Statement 9D

Regular follow-up colonoscopies could be carried out, because surveillance colonoscopy may permit earlier detection of CRC, with a corresponding improved prognosis [EL 3a, RG B]

Randomised controlled trials have not been performed to prove whether surveillance colonoscopy is effective. However, a large number of case series have suggested a benefit of surveillance colonoscopy.<sup>90–94</sup> In a retrospective study of

40 patients with UC associated CRC, Giardiello reported that the CRC was detected at a statistically significantly earlier stage when patients were diagnosed in a surveillance programme (Dukes A/B: 67% vs. 9%).<sup>95</sup>

Three case-control studies have addressed this issue. In a population-based, nested case-control study of 142 patients with UC (derived from a study population of 4664 patients) from Stockholm, Sweden, 2 of 40 patients with UC and CRC and 18 of 102 controls had undergone at least one surveillance colonoscopy (RR, 0.29; 95% CI, 0.06–1.31). Twelve controls, but only one patient with UC-CRC, had undergone 2 or more surveillance colonoscopies (RR, 0.22; 95% CI, 0.03–1.74). Although not statistically significant, the investigators suggested that frequent colonoscopy protects against CRC.<sup>96</sup> In 1990 Lashner et al. reported that 4 of 91 patients who underwent surveillance died of CRC, as compared to 2 of 95 patients who did not undergo surveillance (RR, 2.09; 95% CI, 0.39–11.12). Colectomy was less common in the surveillance group (33 vs. 51;  $p < 0.05$ ). It was performed, on average, 4 years later (after 10 years of disease) in the surveillance group.<sup>97</sup> Finally, Choi et al. examined 41 patients who developed CRC between 1974 and 1991.<sup>98</sup> In this outcome study, 19 patients who underwent colonoscopic surveillance presented with a significantly earlier stage of cancer compared to 22 patients who did not participate in a colonoscopic surveillance programme ( $p = 0.039$ ). The 5-year survival rate was 77.2% in the surveillance group and 36.3% in the non-surveillance group.

In the Cochrane pooled data analysis of these 3 studies, 8 of 110 patients in the surveillance group died of CRC compared to 13 of 117 patients in the non-surveillance group (RR, 0.81; 95% CI, 0.17–3.83).<sup>99</sup> The Cochrane analysis concluded the following: 'there is no clear evidence that surveillance colonoscopy prolongs survival in patients with extensive colitis. There is evidence that cancers tend to be detected at an earlier stage in patients who are undergoing surveillance, and these patients have a correspondingly better prognosis, but lead-time bias may contribute substantially to this apparent benefit. There is indirect evidence that surveillance is likely to be effective at reducing the risk of death from IBD-associated CRC and indirect evidence that it may be acceptably cost-effective<sup>99</sup>.

More recently, in a study from the Netherlands a total of 149 patients with IBD-associated CRC were identified.<sup>100</sup> Twenty-three had colonoscopic surveillance before CRC was discovered. The 5-year CRC-related survival rate of patients in the surveillance group was 100% compared with 74% in the non-surveillance group ( $p = 0.042$ ). In the surveillance group, only one patient died as a consequence of CRC compared with 29 patients in the control group ( $p = 0.047$ ). In addition, more early tumour stages were found in the surveillance group ( $p = 0.004$ ). These results provide evidence for improved survival from colonoscopic surveillance in IBD patients by detecting CRC at a more favourable tumour stage.

### 9.2.3. Initial screening colonoscopy and surveillance schedules

#### Statement 9E

In all patients with UC irrespective of the disease activity, a screening colonoscopy could be carried

out 6–8 years after the beginning of symptoms in order to assess the patient's individual risk profile [EL 5, RG D]

#### Statement 9F

When disease activity is limited to the rectum without evidence of previous or current endoscopic and/or microscopic inflammation proximal to the rectum, inclusion in a regular surveillance colonoscopy programme is not necessary [EL2a, RG B]

#### Statement 9G

In cases with concurrent primary sclerosing cholangitis (PSC), surveillance colonoscopies should be carried out yearly from the point of PSC diagnosis irrespective of disease activity and extent [EL3a, RG B]

#### Statement 9H

The CRC risk profile should be determined at the screening colonoscopy or the first surveillance colonoscopy 6 to 8 years after the first manifestation. Risk stratification mainly depends on extent of disease, severity endoscopic and/or histological inflammation, pseudopolyps, concurrence of PSC, and family history of CRC [EL2b, RG B]

#### Statement 9I

The individual risk profile dictates surveillance colonoscopy intervals: every 1–2 years (high-risk) or every 3–4 years (low-risk) from the eighth year after the first manifestation in both extensive UC and left-sided UC [EL5, RG D]

The CRC risk profile can be determined at the screening colonoscopy or at the first surveillance colonoscopy 8 years after disease onset. Risk stratification mainly depends on four items (e.g. each of these items to be counted with one point): Pancolitis, endoscopic and/or histological inflammation, pseudopolyps and family history of CRC (low-risk 0–2 and high-risk 3–4 points). Ongoing surveillance colonoscopy should be carried out based on the individual risk profile either every 1–2 years (high-risk) or every 3–4 years



(low-risk) from the eighth year after the disease onset in cases of extensive UC as well as in cases of left-sided UC. If there is no evidence of IEN or endoscopic and/or histological inflammation in two consecutive surveillance colonoscopies the surveillance interval may be increased (e.g. from every 1–2 years to every 3–4 years).

A meta-analysis suggests that follow-up colonoscopies may reduce the risk of dying of a colitis-associated colon carcinoma and are cost-effective. This is based on the fact that colitis-associated colon carcinomas are recognised earlier, although interval carcinomas may occur, nonetheless.<sup>99</sup>

The risk of developing a carcinoma increases with the duration of disease and the disease extent, therefore regular monitoring should start earlier in the case of pancolitis than left-sided or distal colitis. Of note, a Dutch study recently pointed out that up to 22% of patients that develop a colitis-associated colon carcinoma do so prior to commencing surveillance colonoscopies.<sup>79</sup> If patients suffering from PSC are excluded – as they should be monitored from the time of PSC diagnosis – the carcinomas “missed” are reduced to approximately 15%. Considering this and knowing that a pancolitis may develop from inflammation described initially as a distal colitis without overt clinical symptoms, a full colonoscopy with multiple biopsies should be carried out within 6–8 years after the first symptoms of disease in order to establish the endoscopic and/or microscopic extent of disease and to pace subsequent endoscopic surveillance.

The monitoring interval should vary from 1 to 4 years according to the individual risk profile to prevent the development of interval carcinomas.<sup>93,101,102</sup> As the risk for CRC is only minimally increased in patients with proctitis (with no other risk factors), no regular monitoring is required in this group. In contrast, the risk of developing a carcinoma in patients with ulcerative colitis and PSC is not only five times higher,<sup>103</sup> but has been reported to occur early (median 2.9 years) in the course of the disease<sup>104</sup> with carcinomas frequently occurring on the right-hand side of the colon.<sup>105</sup> Therefore, patients should be monitored annually from the diagnosis. After sub-total colectomy with an ileorectal anastomosis or restorative proctocolectomy, carcinomas may occur in the remaining colonic mucosa distally to the anastomosis or within the pouch.<sup>106</sup> Therefore, the remaining colon and/or the pouch should be monitored at regular intervals.

### 9.3. Colonoscopic procedures

#### Statement 9J

Good bowel preparation is essential for effective surveillance colonoscopy. If faecal residue is present, repeat colonoscopy should be considered [EL5, RG D]

#### Statement 9K

Colonoscopic surveillance is best performed when ulcerative colitis is in remission, because it is

otherwise difficult to discriminate between dysplasia and inflammation on mucosal biopsies [EL5, RG D]

Surveillance colonoscopies aim to detect neoplasia with a high sensitivity and specificity. If possible, surveillance colonoscopies should be carried out in remission, because remaining inflammatory activity could be misinterpreted as intra-epithelial neoplasia. Similar to screening colonoscopies in the otherwise healthy population, the quality of the preparation will significantly affect the detection rate of lesions.<sup>107</sup> In addition, there is a correlation between the withdrawal time and the detection rate of neoplasias.<sup>108</sup>

#### Statement 9L

Chromoendoscopy with targeted biopsies is the surveillance procedure of choice for appropriately trained endoscopists [EL1b, RG B]. Alternatively, random biopsies (quadrant biopsies every 10 cm) and targeted biopsies of any visible lesion should be performed if white light endoscopy is used [EL3, RG B]

Several studies performed during the last few years have demonstrated that most intraepithelial neoplasias (IEN) can be visualised by high-resolution endoscopy, either as irregular mucosa, strictures or mucous membrane elevations<sup>109–111</sup> Therefore, it is very important to take targeted biopsies from all visible suspicious lesions. In addition, in order to assess disease extent and mucosal healing it is useful to take 2 biopsies from each colonic segment. Using white light colonoscopy alone, IEN may not be visible macroscopically (about 20%): Rubin et al. were able to demonstrate in a mathematical model that at least 34 “blind” biopsies are required to achieve a 90% confidence interval for detection of carcinomas with 64 biopsies reaching a 95% confidence interval.<sup>112</sup> Therefore, we recommend taking four biopsies every 10 cm in order to achieve a 90% certainty of detection, although chromoendoscopy by an appropriately trained endoscopist is the preferred procedure.

Using mathematical modelling Awais<sup>113</sup> calculated the confidence level with which dysplasia can be excluded, the dysplastic field size detection threshold, the predicted area of a dysplastic field, and the number of biopsies needed for a given dysplasia detection threshold and confidence level. In this model, 32 random biopsies provide only 80% confidence that dysplasia involving  $\geq 5\%$  of the colon can be detected. In order to have 90% confidence of achieving a dysplasia detection threshold equal to enhanced endoscopy (10 mm diameter circle with an area of 0.785 cm<sup>2</sup>) 4690 random biopsies are required. When one single biopsy out of 18 is dysplastic, this predicts a dysplastic area (89 cm<sup>2</sup>) several orders of magnitude greater than dysplastic fields that are readily detectable by enhanced endoscopy (1 cm diameter), and the predicted field size increases rapidly with multiple positive biopsies.

The enhanced ability to detect IEN with high-resolution endoscopy makes the strategy of taking random biopsies controversial. Furthermore, a survey on the implementation of the recommendation of 40–50 random biopsies in surveillance colonoscopies in Germany revealed that only 9.2% of the surveillance colonoscopies were performed in accordance with the guidelines.<sup>114</sup> The same issue with adherence to surveillance guidelines has been reported in several other countries.<sup>115–117</sup> The futility of taking random biopsies is also highlighted by the fact that IEN was detected by random biopsy extremely rarely in studies comparing conventional colonoscopy with chromoendoscopy (KieSSLich 2003: 2 IEN in 5,098 random biopsies,<sup>118</sup> Rutter 2004: 0 IEN in 2,906 random biopsies<sup>119</sup> and Dekker 2007: 1 IEN in 1,522 random biopsies<sup>120</sup>). The preferred alternative is to perform chromoendoscopy (indigo carmine or methylene blue) with targeted biopsies. In two prospective, single centre studies more IEN was discovered with biopsies using chromoendoscopy than by white light endoscopy.<sup>118,119</sup> Furthermore Hurlstone<sup>121</sup> reported, that high-magnification, indigo carmine-assisted chromoendoscopy can improve the detection of intraepithelial neoplasia in the endoscopic screening of patients with ulcerative colitis.

The value of high-resolution virtual chromoendoscopy (NBI, FICE, iScan) with targeted biopsies has not been sufficiently resolved.<sup>120</sup> Therefore this should not be used as the surveillance strategy. Nevertheless, it is still unclear how much technical experience is required to perform adequate chromoendoscopy and whether the latest generation of endoscope combining HDI and/or HDTV will permit a similarly high IEN detection rate.

## 9.4. Chemoprevention

### 9.4.1. 5-ASA and CRC

Chemopreventive agents are used to inhibit, delay or reverse carcinogenesis. 5-Aminosalicylates (5-ASA) are considered to reduce the risk of colorectal cancer in patients with UC in cohort and case–control studies. A randomised controlled trial specifically designed to confirm this effect is not feasible given the prohibitive number of patients at risk that would need to be enrolled in each arm (1000 to 3000 according to base-case cancer incidences<sup>78</sup> and projected risk reduction (30 to 50%)). In the meta-analysis by Velayos et al., 3 cohort studies<sup>122–124</sup> and 6 case–control studies published<sup>84,93,125,126</sup> or presented<sup>127</sup> up to January 2004 were reviewed.<sup>87</sup> The risk of CRC was halved in patients exposed to 5-ASA and this reduction was statistically significant (OR 0.51, 95% CI 0.37–0.69). Seven studies have been fully published thereafter.<sup>82,86,127–130</sup> However, four of them do not differentiate the risk of CRC from that of other forms of advanced dysplasia (CRC and high-grade dysplasia)<sup>82</sup> or all forms of dysplasia.<sup>86,87,127</sup> In 2006 Velayos assessed the risk factors for 188 cases of CRC (in patients with UC seen at the Mayo Clinic from 1976 to 2002).<sup>87</sup> In the final multivariate model a significant reduction in the risk of CRC associated with an exposure to 5-ASA of at least 1 year (OR 0.4, 95% CI 0.2–0.9) was confirmed. Two further studies were based on the number of 5-ASA prescriptions in large Health Care databases.<sup>128,129</sup> van Staa et al. suggested from the GPRD database that a regular use of 5-ASA within the year preceding the diagnosis of CRC was associated with a significant reduction in the risk.

Similarly, Terdiman et al. found a trend ( $p=0.08$ ) toward a decreased risk of CRC with increasing number of 5-ASA prescriptions within the year preceding the diagnosis of CRC. However, Bernstein et al. have updated the negative case–control study from the Manitoba database<sup>126</sup> and still found no favourable effect of 5-ASA. Of note, in this cohort, the disease extent was not reported and the updated analysis was not adjusted for the propensity to receive 5-ASA (although this treatment has probably been specifically prescribed in patients at highest risk of CRC for the purpose of chemoprevention in the last few years). In conclusion, when updating the literature, there is no definite reason to challenge the previous statement that 5-ASA may reduce the incidence of CRC in patients with UC.<sup>131</sup>

### 9.4.2. Patient selection for chemoprevention with 5-ASA

Besides an individual context (such as PSC or a family history of CRC) that may justify endoscopic surveillance and chemoprevention from diagnosis<sup>131–134</sup>, the three main determinants of excess risk of CRC in patients with UC are the duration of the disease, the cumulative extent of the disease at any time and chronic macroscopic<sup>110</sup> and microscopic<sup>80,85</sup> inflammation of the colonic mucosa.<sup>131–134</sup> The question whether the protective effect of 5-ASA on the CRC risk is different in patients with known risk factors for dysplasia or cancer has not been addressed in the literature. In a case–control study nested in the CESAME cohort, adjusted for the propensity of receiving 5-ASA, a subanalysis was performed in IBD patients with or without longstanding (>10 years) extensive (>50% of colonic mucosa at any time) colitis.<sup>135</sup> The protective odds-ratio was significant for patients with longstanding extensive colitis (OR 0.5, 95% CI 0.2–0.9) while it was not in the remaining patients (OR 0.8, 95% CI 0.3–1.7). However, the published statements on the chemopreventive effect of 5-ASA in UC are not restricted to particular situations (such as longstanding and/or extensive colitis),<sup>131–133</sup> which justifies lifelong chemoprevention from diagnosis in all patients, except for those ongoing isolated proctitis. Many arguments can be listed for legitimating this position: first, a significant proportion of CRC are diagnosed within the first years after the diagnosis, even if a significant proportion of them are likely to be sporadic cases; second, it is established that carcinogenesis of sporadic and inflammation-related CRC is quite different,<sup>134,136</sup> but given the multiplicity of potential molecular mechanisms of action of 5-ASA on carcinogenesis,<sup>137</sup> it is theoretically possible that 5-ASA may have a chemopreventive effect in sporadic CRC as well as in inflammation-driven cancers; third, inflammation appears as an independent important driver for UC-related CRC,<sup>80,84,85,111,133</sup> and it has not been feasible up to now in routine practice to sequentially test for macroscopic and microscopic mucosal healing in order to stratify the impact of chemoprevention according to the inflammation status; finally, one observational cohort study suggested that 5-ASA is not able to significantly decrease the progression from low-grade dysplasia to more advanced stages of neoplasias,<sup>138</sup> and the studies assessing specifically the relation between current exposure to 5-ASA and the risk of dysplasia failed to demonstrate, taking into account a more limited statistical power, a signal toward a chemopreventive effect of 5-ASA on dysplasia.<sup>82,84,123,131</sup> This raises the hypothesis that 5-ASA

given from the onset of the disease and for prolonged periods impacts on early steps of inflammation-related carcinogenesis.

#### 9.4.3. Immunosuppressants

Immunomodulators (thiopurines and methotrexate) and biologics (anti-TNF) could theoretically either increase the risk of CRC via immunosuppression, or be chemopreventive via a reduction of chronic mucosal inflammation. There are no data for methotrexate and anti-TNF and the data for thiopurines conflict.<sup>84,85,87,122,129,139,140</sup> These included the only published study specifically designed to address the chemopreventive effect of thiopurines on the risk of CRC in IBD.<sup>140</sup> There is no evidence for a specific antineoplastic action of thiopurines thus one must assume that thiopurines would diminish the risk of colorectal cancer mainly via an anti-inflammatory effect. If this is true, the effect of thiopurines should be best demonstrated in the subgroup of patients at most risk of inflammation-driven CRC, namely patients with longstanding extensive colitis. The proportion of IBD patients at high risk of CRC in stable clinical remission on thiopurines who have no persistent mucosal microscopic inflammation (i.e. the good candidates for the chemopreventive effect of thiopurines) is low,<sup>141</sup> and it is currently impossible to perform subanalysis of such patients in clinical epidemiological studies.

When analysing published series in detail, the use of thiopurines<sup>80,84,85,87,122,129,139,140</sup> appears restricted to the most severe patients in a classical step-up approach, raising the hypothesis that patients exposed to thiopurines had a level of chronic colonic inflammation at least as severe as patients not exposed. As an illustration, in the study by Matula et al.,<sup>140</sup> patients exposed to thiopurines were more prone to receive corticosteroids or require surgery suggesting a greater mean intrinsic "inflammatory severity." In the nested case-control study Olmsted population,<sup>87</sup> less than 10% of the case and control patients were exposed to thiopurines. This rate was <1% in the study by Terdiman et al.,<sup>129</sup> suggesting again drugs were used only in the most severe patients. A more relevant insight may come from tertiary care or population-based cohorts with an early and extensive use of thiopurines, which therefore include a significant proportion of stable responders with no persistent inflammation. In the prospective observational CESAME cohort, one third of the patients were exposed to thiopurines, and it was possible to show in a subgroup of the cohort that the overall yearly clinical activity of IBD in patients exposed to thiopurines was not higher than in patients naïve to immunosuppression.<sup>142</sup> In this cohort, thiopurine use was associated with a three-fold reduction in the risk of advanced neoplasias (high-grade dysplasia and CRC) in IBD patients at high risk of inflammation-driven cancers (longstanding extensive colitis). This trend must be confirmed in other large cohorts with early and extensive use of immunosuppressants.

#### 9.4.4. Other drugs

Patients enrolled in a randomised controlled trial of ursodeoxycholic acid in UC patients with PSC<sup>143</sup> receiving active drug experienced a significant reduction in CRC suggesting that ursodeoxycholic acid should be given to patients with UC and PSC.<sup>131–133</sup> Folic acid supplements,

calcium, multivitamins, or statins have not been consistently associated with lower rates of CRC in UC, and no important study in this field has been published since the first evidence-based European consensus on the management of UC.<sup>131</sup>

#### Statement 9M

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]. There is insufficient evidence to recommend for or against chemoprevention with thiopurines

### 9.5. Management of dysplasia

Therapeutic recommendations for management of dysplasia in UC are based on macroscopic pattern (flat or elevated) and microscopic characteristics of the lesion (indefinite, low grade or high grade).<sup>111,144,145</sup>

#### 9.5.1. Microscopic patterns of dysplasia

The current, widely used definition of dysplasia was proposed by Riddell et al. in 1983.<sup>145</sup> Dysplasia was defined as unequivocal neoplasia of the epithelium confined to the basement membrane, without invasion into the lamina propria. Dysplasia is the best and most reliable marker of an increased risk of malignancy in patients with IBD.<sup>146</sup>

Dysplasia (intraepithelial neoplasia—IEN) is now generally classified according to the grade of neoplastic change into 3 morphologic categories: "indefinite," "low grade" (LGD), or "high grade" (HGD).<sup>145</sup> However, dysplasia almost certainly evolves along a progressive (continuous) scale rather than in discrete categories. This contributes to the significant degree of variability in interpretation of the grade of dysplasia even among experienced gastrointestinal pathologists.<sup>147,148</sup> Levels of agreement are highest for the category of HGD and for specimens considered negative for dysplasia, and lower for specimens in the indefinite and LGD categories. These limitations in the assessment of dysplasia have led to the recommendation that histological slides should be reviewed by a second expert gastrointestinal pathologist.

#### 9.5.2. Macroscopic patterns of dysplasia

#### Statement 9N

Endoscopically visible dysplastic raised lesions within an area within the extent of ulcerative colitis can be divided in adenoma-like and non-adenoma-like by their macroscopic characteristics [EL 2a, RG B]



**Statement 90**

Presence of low grade or high grade dysplasia should be confirmed by an external second pathologist [EL 1b, RG B]

There is inconsistency in the literature about the definitions used to designate the macroscopic characteristics of dysplastic lesions in UC.<sup>111,144</sup> Some studies categorise dysplastic lesions as flat only if they are endoscopically undetectable, whereas others include visible plaque-like or slightly raised areas of mucosa in this category also. For the purpose of this evidence-based consensus, flat dysplasia refers to endoscopically undetectable lesions, whereas raised dysplasia refers to any type of endoscopically detectable lesions.

Raised lesions with dysplasia (RLD) in UC have been broadly separated into those that appear similar to non-IBD related sporadic adenomas, referred to as “adenoma-like,” and those which do not resemble adenomas: “non-adenoma-like” (the former term “DALM”).<sup>149</sup> Adenoma-like RLDs represent well circumscribed, smooth or papillary, nonnecrotic, sessile, or pedunculated polyps that are usually amenable to removal by routine endoscopic methods.<sup>133,134</sup> Non-adenoma-like lesions include velvety patches, plaques, irregular bumps and nodules, wart-like thickenings, stricturing lesions, and broad-based masses,<sup>111,149–151</sup> and are not usually amenable to removal by colonoscopic polypectomy. Non-adenoma, and adenoma-like RLDs are differentiated on the basis of their gross (endoscopic) appearance. Histological features may be helpful,<sup>152</sup> although both types of lesions may appear identical.<sup>153,154</sup>

Polyps with dysplasia arising proximal to the macroscopic and histologic involvement by the chronic inflammatory process are considered sporadic and should be treated accordingly.

**9.5.3. Management of raised dysplasia****Statement 9P**

Adenoma-like raised lesions can be adequately treated by polypectomy provided the lesion can be completely excised shows absence of dysplasia at the margins of the specimen, and there is no evidence of flat dysplasia elsewhere in the colon, either adjacent to, or distant from, the raised lesion [EL 2a, RG B]

**Statement 9Q**

Patients with non-adenoma-like raised lesions should undergo a colectomy, regardless of the grade of dysplasia detected on biopsy analysis because of the high association with metachronous, or synchronous, carcinoma [EL 2a, RG B]

**Statement 9R**

Polyps with dysplasia that arise proximal to the segments with macroscopic or histologic involvement are considered as sporadic adenomas and should be treated accordingly [EL 2c, RG B]

Adenoma-like RLDs can be adequately treated with polypectomy and continued surveillance. Four studies have shown no significant difference in the incidence of polyp detection on follow-up between patients with UC and an adenoma-like RLD and patients with UC and a sporadic adenoma, or between either of these two groups of UC patients and a non-UC sporadic adenoma control group.<sup>111,152,155,156</sup> In one study, 70 dysplastic polyps were resected from 48 patients; during a mean follow-up period of 4.1 years, colonoscopies revealed additional polyps in 48% but none developed carcinoma.<sup>156</sup> Another study included 34 UC patients, 24 with adenoma-like RLDs and 10 with sporadic adenomas, 28 of which were treated by polypectomy; 58.8% of patients with adenoma-like RLDs developed at least one further adenoma-like RLD on follow-up evaluation, one patient had flat low-grade dysplasia, which was resected within 6 months of the initial polypectomy, and another patient, with primary sclerosing cholangitis, developed adenocarcinoma 7.5 years after initial polypectomy. There was no significant difference in the prevalence of polyp formation on follow-up evaluation between UC patients with an adenoma-like RLD (62.5%) and UC patients with a sporadic adenoma (50%), or between either of these two UC patient subgroups and a non-UC sporadic adenoma control group (49%).<sup>155</sup> Another study of 40 patients undergoing endoscopic resection of adenoma-like RLDs reported one case of adenocarcinoma after a mean follow-up period of 4.2 years<sup>111</sup> this was not significantly different from the frequency of cancer within the surveillance population as a whole. Finally, in one recent follow-up study including 148 patients with UC adenoma-like lesions, 87 patients were treated with polypectomy; during a mean follow-up period of 6 years only 4.6% developed dysplasia (2 of which were ultimately diagnosed with carcinoma).<sup>152</sup>

Biopsies should be taken from the flat mucosa surrounding any dysplastic polyp to assess whether it is involved in the chronic inflammatory process and also to assess whether there is any dysplasia in the surrounding flat mucosa. If an adenoma-like RLD<sup>111,152,155–157</sup> is detected within an area of inflammation it can be treated conservatively by polypectomy provided the lesion can be completely excised, shows absence of dysplasia at the margins of the specimen, and there is no evidence of flat dysplasia elsewhere in the colon, either adjacent to, or distant from, the RLD.

There is a strong association of metachronous or synchronous carcinoma with non-adenoma-like RLDs, ranging from 38% to 83%.<sup>144</sup> For this reason, it is generally recommended that patients with UC and an endoscopically unresectable non-adenoma-like RLD should undergo a colectomy, regardless of the grade of dysplasia detected on biopsy analysis. However endoscopic mucosal resection has been used for treatment of non-adenoma-like lesions in



UC. In the largest series reporting on the outcome of this approach, there was a larger recurrence rate compared to endoscopic mucosal resection for sporadic lesions (14% vs. 0%, respectively) after a median follow-up of 4.8 years.<sup>158</sup> Finally, if a dysplastic polyp occurs in an area proximal to the microscopic level of inflammation, with no dysplasia in flat mucosa, it can be regarded as a sporadic adenoma and treated accordingly.<sup>156,159</sup>

#### 9.5.4. Management of flat dysplasia

##### Statement 9S

Flat high-grade dysplasia warrants a recommendation of colectomy because of the risk of a concomitant or future colorectal cancer [EL 2a, RG B]

##### Statement 9T

The current evidence is insufficient to assess the balance of risks and benefits of colectomy for flat low-grade dysplasia. The decision to recommend colectomy or continued surveillance is best tailored to the individual after careful discussion [EL 5, RG D]

Current evidence indicates that at the time flat HGD dysplasia is discovered, CRC may already be present in 42% to 67% of cases, although this estimation is based on three studies that include a limited number of cases with HGD (from 6 to 24 patients).<sup>102,160,161</sup> Furthermore, a review of 10 prospective surveillance trials found that 15 of 47 patients (32%) with HGD developed CRC upon further follow-up,<sup>160</sup> and updated data from the St Mark's surveillance programme indicated that 2 of 8 patients (25%) with HGD who did not have immediate colectomy, progressed to CRC.<sup>78</sup> Overall, the immediate and subsequent risk of CRC in patients with flat HDG is large enough to warrant a recommendation for colectomy.

Recommendations on the optimal management of UC patients with flat LGD are more controversial, in part because not every study reporting the outcome of LGD distinguished between raised and flat lesions. Although the rate of synchronous CRC is lower for LGD than HDG, it is still considerable. Results of three studies including 10, 11 and 16 patients with LGD identified CRC in colectomy specimens in 20%, 27% and 19%, respectively.<sup>78,160,162</sup> A meta-analysis of 20 surveillance studies analysed the cancer risk of 477 patients with flat LGD and 31 patients with LGD in a RLD.<sup>163</sup> The incidence of CRC was 14 per 1000 patient-years. For HGD and/or CRC, it was 30 per 1000 patient-years. The positive predictive value of flat LGD was 22% for synchronous CRC and 36% for synchronous HGD and CRC. The positive predictive value for progression to HGD and CRC was 14.6%. If LGD was detected in a RLD, the rates of

synchronous and metachronous cancer were higher. Overall, when LGD is detected on surveillance, there is a 9-fold increased risk of developing CRC, and a 12-fold risk of developing HGD or CRC.<sup>163</sup>

Estimates for the risk of progression from LGD to HGD and CRC, if the lesions are left in place, vary among published studies. The aforementioned meta-analysis indicated that the positive predictive value is approximately 14.6% for progression of flat LDG to HGD and/or CRC, with significant variability present between studies.<sup>163</sup> High rates of progression have generally been reported in retrospective studies, ranging from 23% on an updated 30-year follow-up from the St Mark's hospital to 33% and 53% 5-year progression in series from the Mayo Clinic<sup>164</sup> and Mt Sinai New York<sup>162</sup> hospitals, respectively. In contrast, other prospective studies have reported lower rates of progression in patients with LGD. One study found only a 3% initial, and 10% subsequent, rate of progression to CRC during a 10-year follow-up period. Since these rates were not significantly higher than the 0.8% and 3% progression rates among patients without dysplasia, this observations suggests that LGD may not be associated with a higher risk of CRC.<sup>101</sup> Likewise, a prospective Swedish study found no progression to CRC, and only 2 cases of progression to HGD, over a 10-year period.<sup>165</sup> Furthermore, a summary of 8 studies revealed that after a diagnosis of LGD was made, subsequent surveillance, with an average of 4.3 colonoscopies per patient, detected more HGD lesions ( $n=47$ ) than CRCs ( $n=18$ ) or RLDs ( $n=8$ ).<sup>163</sup> This may be important if one considers the goal of surveillance to be the prevention of mortality from CRC rather than the detection of HGD.

There may be a difference in natural history of LGD depending on whether dysplasia is found on the initial screening colonoscopy (prevalent dysplasia) or during surveillance colonoscopy (incident dysplasia). A review of 10 prospective studies reported that HGD or CRC developed in 15/55 patients with prevalent dysplasia (29%) in comparison with 33/204 (16%) of those with incident dysplasia.<sup>160</sup> As for the relevance of focality of dysplasia, it has been sometimes assumed that unifocal lesions would be at lower risk of progression than multifocal dysplasia. However, a recent study found that the overall 5-year progression rate of flat LGD to either HGD or CRC was similar in unifocal and multifocal dysplasia.<sup>164</sup>

The current evidence is insufficient to assess the balance of risks and benefits of colectomy for flat LGD. Thus, the decision to undergo colectomy versus continued surveillance in patients with flat LGD should be individualised and discussed at length between the patient, the gastroenterologist and the colorectal surgeon. Colectomy will eradicate the risk of CRC, but if a patient is unwilling to undergo colectomy, yearly surveillance is recommended.<sup>133</sup>

## 10. Psychosomatics

### 10.1. Introduction

The controversies about the role of psychosocial factors in UC have been addressed in systematic reviews.<sup>166–169</sup> A biopsychosocial model<sup>170,171</sup> represents an advantage over

a biomedical model, because it embodies the complex biological and psychosocial interactions that explain human illness. 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.

## 10.2. Influence of psychological factors on disease

### 10.2.1. Etiology

#### Statement 10A

There is no conclusive evidence for anxiety, depression and psychosocial stress contributing to risk for UC onset [EL2c, RG D]

A retrospective nested case-control study with 12,500 participants examined temporal relationships without potential recall bias, limited to patients with UC who obtained treatment for depression or anxiety before UC diagnosis. A significant association was found between depression and UC (OR 1.49, 95% CI 1.12–1.93) when the depression predated UC by more than 5 years, which is unlikely to be influenced by initial UC symptom presentation.<sup>172</sup> Prospective studies on psychosocial stress as a risk for UC onset have not been conducted until now.

### 10.2.2. Course of disease

#### Statement 10B

Psychological factors may have an impact on the course of UC. Perceived psychological stress [EL2a, RG B] and depression [EL2a, RG B] are risk factors for relapse of the disease. Depression is associated with low health-related quality of life [EL3a, RG B]. Anxiety is associated with non adherence with treatment [EL4, RG C]

A systematic review demonstrated an association between psychological stress and disease activity in patients with UC.<sup>167</sup> Another systematic review reported a significant relationship between stress and inflammation in 4 longitudinal studies assessing the impact of stress or depression on disease course.<sup>169</sup> A prospective study demonstrated that only high perceived stress (adjusted OR=2.40, 95% CI, 1.35–4.26) was significantly associated with symptomatic flares.<sup>173</sup> Higher anxiety and depression at baseline were related to more frequent relapses in the follow-up period in a second prospective study.<sup>174</sup> Another study did not find an increased risk of relapse in patients diagnosed with depressive disorder by a psychiatric interview.<sup>175</sup> Depression<sup>176,177</sup> and neuroticism<sup>178</sup> were associated with low health-related quality of life. Anxiety and

moodiness were associated with nonadherence with UC-treatment.<sup>179</sup>

## 10.3. Psychological disturbances in ulcerative colitis

#### Statement 10C

Psychological distress and mental disorder are more common in patients with active ulcerative colitis than in population-based controls, but not in patients in remission [EL3a, RG B]

#### Statement 10D

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

A systematic review demonstrated that anxiety and depression are associated with disease activity. However, the prevalence of mental disorders (anxiety and depressive disorders) in patients with active disease is comparable with the one of patients with other chronic somatic diseases.<sup>176</sup> Patients in remission do not differ in the amount of psychological distress and the frequency of mental disorders (anxiety and depressive disorders) from general population controls.<sup>180</sup> There are contradictory findings on the association between gender and depression in patients with active UC.<sup>180–182</sup> A consistent association between anxiety and depressed mood and the prevalence of IBS-like symptoms in patients in remission has been reported.<sup>183–185</sup>

## 10.4. Approach to psychological disorders

### 10.4.1. Communication with patients

#### Statement 10E

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 [EL3b, RG B]. Patients' disease control can be improved by combining self-management and patient-centred consultations [EL1b, RG B]

Health perceptions impact on the experience of the illness.<sup>186</sup> Increasing physician awareness of the fact that psychologically distressed patients have difficulty in processing clinically relevant information<sup>187</sup> may lead to

improved doctor–patient communication.<sup>188</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>189</sup> Since approximately half of the patients in IBD referral centres use the internet to gather IBD-related information,<sup>190,191</sup> web-based communication programmes seem to be feasible and to increase the level of disease specific knowledge.<sup>192</sup> Psychosocial factors are strongly correlated with health care utilization.<sup>193</sup> Medical non-adherence has been reported in over 40% of patients, and this is a situation in which the patient-doctor relationship also plays a key role.<sup>194</sup> Self-management guidebooks together with patient-centred consultations improve patients' disease control.<sup>195,196</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>197</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 effect.<sup>198–202</sup>

#### 10.4.2. Psychological support

##### Statement 10F

Physicians should screen patients for anxiety, depression and need for additional psychological care and recommend psychotherapy if indicated [EL 2b, RG B]. Patients should be informed of the existence of patient associations [EL 5, RG D]

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>193</sup> A validated questionnaire based on inflammatory bowel disease is available to assess the demand for psychological care.<sup>203,204</sup> Approximately one third of patients attending an IBD centre express a need for psychological intervention.<sup>204</sup> Anxiety, younger age as well as impaired social support increased this demand. Detection and treatment of psychological distress has the potential to improve health-related quality of life.<sup>205</sup> 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>206</sup> and the Rating Form of Inflammatory Bowel Disease Patient Concerns (RFIPC).<sup>207</sup> Since strategies aimed at improving social support can have a favourable impact on psychological distress,<sup>208,209</sup> training gastroenterologists to integrate psychosocial factors in clinical practice is important. Because patients describe deficiencies in the care of family members, insufficient information and inadequate access to healthcare resources,<sup>210</sup> integrated psychosomatic care should be available. Integrated psychosomatic care can be defined as a combined somatic (gastroenterology) and psychological (psychotherapist, psychologist, psychiatrist) care of patients, especially in tertiary centres.

#### 10.4.3. Therapeutic intervention

##### Statement 10G

Psychotherapeutic interventions are indicated for psychological disorders and low quality of life associated with ulcerative colitis [EL 1b, RG B]

Some studies have shown that psychotherapy and relaxation methods have a positive influence on the psychological dimensions of the illness such as psychological well-being, coping strategies, quality of life and psychological distress<sup>211–216</sup> as well as perception of pain.<sup>217</sup> The effects of psychosocial interventions on quality of life, coping, emotional state and disease activity in ulcerative colitis were assessed in a systematic review.<sup>218</sup> The authors concluded that psychotherapeutic interventions in general, if applied to unselected patients, are not likely to have a relevant positive effect. Therefore, the diagnosis of ulcerative colitis is insufficient alone to recommend psychotherapy in adult patients, but in adolescents, psychological interventions may be beneficial.<sup>218</sup>

#### 10.4.4. Therapeutic choice

##### Statement 10H

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,<sup>216,217</sup> 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>219</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.

### 11. Extraintestinal manifestations of ulcerative colitis

#### 11.1. Introduction

Extraintestinal manifestations (EIMs) are common in UC affecting up to 35% of patients.<sup>220,221</sup> Detailed prospective studies using adequate diagnostic criteria are rare. Most

reports are retrospective and based on review of patients' files. The occurrence of one EIM often seems to predispose to others. The activity of certain EIMs such as peripheral arthritis, erythema nodosum, oral aphthous ulcers and episcleritis are related to UC activity. In contrast, pyoderma gangrenosum, uveitis, axial arthropathy and primary sclerosing cholangitis (PSC) usually run an independent course.

For those EIMs whose activity mirror the colitis, treatment can parallel that of the underlying disease. Treatment otherwise is mainly on a case by case basis as RCTs are lacking. This section concentrates on the more frequently encountered EIMs for which at least some quantifiable data exist, and does not include systemic consequences of severe UC such as iron deficiency or malnutrition.

#### Statement 11A

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 [EL2b, RG B]. Axial arthritis, including sacro-iliitis 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 B27 is over-represented in axial arthritis related to UC this is not of diagnostic value [EL2b, RG B]

## 11.2. Arthropathy

### 11.2.1. Peripheral arthropathy

The Oxford group subclassified peripheral arthropathy into type I and type II, but only type I is associated with intestinal disease activity.<sup>222</sup> Type I is pauciarticular and affects large (predominantly weight bearing) joints including the ankles, knees, hips, wrists and sometimes elbows and shoulders. By convention less than five joints are affected. The arthritis is acute, self limiting (weeks rather than months) and typically asymmetric. This arthropathy is observed in 4–17% of patients with UC. Type II is a polyarticular arthritis mainly affecting the small joints of the hand but independent of UC activity and is observed in 2.5% of patients with UC.<sup>222</sup> The diagnosis of arthritis is made clinically from the finding of painful swollen joints (synovitis). The differential diagnosis includes osteoarthritis, rheumatoid arthritis and arthritis associated with connective tissue diseases such as lupus. It has to be differentiated from arthralgia (which may complicate corticosteroid withdrawal), osteonecrosis related to corticosteroids, and infliximab related lupus-like syndrome.<sup>223</sup>

### 11.2.2. Axial arthropathy

Axial arthropathy includes sacroiliitis and spondylitis. Irrespective of the presence of inflammatory back pain,

isolated radiographic sacroiliitis has been found in 25–50% of patients with UC.<sup>224–226</sup> The diagnosis of ankylosing spondylitis (AS) according to the modified Rome criteria<sup>227</sup> includes a chronic inflammatory back pain (at night and at rest, improving by exercise), morning stiffness, limited spinal flexion and, in later stages, reduced chest expansion. Radiographs demonstrate sacroiliitis, syndesmophytes and bone proliferation evolving to ankylosis ("bamboo spine"). While computed tomography is more sensitive for detecting structural abnormalities than simple radiographs, the current gold standard is magnetic resonance imaging due to its ability to demonstrate inflammation before bone lesions occur.<sup>228,229</sup> The overall prevalence of AS in IBD ranges from 4–10%. HLA-B27 is found in 25–75% of patients with UC and ankylosing spondylitis<sup>224,230–232</sup> but only in 7–15% of patients with isolated sacroiliitis. HLA-B27 positive IBD patients seem to be at risk for the development of AS.<sup>232</sup>

### 11.2.3. Treatment of arthropathy related to ulcerative colitis

#### Statement 11B

In peripheral arthritis treatment of the underlying UC is normally effective in relieving symptoms [EL 5, RGD]. For persistent symptoms in the absence of active UC there is general support for use of short term treatment with non-steroidal anti-inflammatory agents. Local steroid injections and physiotherapy are also effective [EL4, RG D]. Sulfasalazine has a role in persistent peripheral arthritis [EL1a, RG B]. In axial arthropathy arguments in favour of intensive physiotherapy [EL2a, RG B], associated with NSAIDs are stronger, but safety concerns mean that long-term treatment with NSAIDs is best avoided if possible [EL1b, RG B]. Sulfasalazine [EL1a, RG B], methotrexate [EL1b, RG B] and azathioprine [EL3b, RG C] are generally ineffective, or only marginally effective. The efficacy of anti-TNF therapy for patients with ankylosing spondylitis and UC intolerant or refractory to NSAIDs is well established [EL1b, RG B]

Recommendations for the treatment of IBD-related arthropathy are based on studies in spondyloarthropathy, predominantly ankylosing spondylitis. No single prospective controlled trial in IBD patients is available in the literature. Only small open-label trials or case reports are published.<sup>233–236</sup>

In peripheral arthritis the emphasis should be on the treatment of the underlying UC, including corticosteroids, immunomodulators and anti-TNF agents as appropriate. Symptomatic relief may be obtained by rest and physiotherapy. Although there is concern that NSAIDs may aggravate the underlying UC<sup>237,238</sup>, this risk seems low, particularly if prescribed at low dose and for short



duration.<sup>239</sup> The use of COX-2 inhibitors such as etoricoxib and celecoxib appears safer with a lower risk of disease flare than conventional NSAIDs.<sup>240,241</sup> A beneficial effect of sulfasalazine on large joint arthropathy has been reported.<sup>242,243</sup> Several open-label studies and some controlled trials have demonstrated an impressive effect of IFX on peripheral arthritis.<sup>244</sup>

Treatment of axial arthropathy in UC is based on evidence from ankylosing spondylitis. It should include intensive physiotherapy. NSAIDs are the mainstay of medical therapy and recommended as first line therapy in AS. However long-term treatment with high-dose NSAIDs is generally inadvisable in patients with UC. The effect of corticosteroids is poorly reported. Local corticosteroid injections can be considered. Sulfasalazine, methotrexate and azathioprine are considered to be ineffective or only marginally effective in AS with axial symptoms.<sup>245</sup> In patients with active AS refractory to or intolerant of NSAIDs, anti-TNF agents are recommended. The efficacy and safety of IFX and ADA in ankylosing spondylitis are now well established.<sup>228,244,246–251</sup>

### 11.3. Metabolic bone disease

Low bone mass and osteoporosis are common in both male and female patients with UC (20%–50%). Contributing factors include chronic inflammation, corticosteroid treatment, age, smoking, low physical activity and nutritional deficiencies.<sup>252</sup> Diagnosis of osteoporosis is best made by a *T* score < -2.5 on bone densitometry (DEXA scanning) in patients over 50 years old and in patients under 50 "low bone mass" is defined by a *Z*-score < 2.0.

#### Statement 11C

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]

The precision and reproducibility of ultrasound and Q-CT is not sufficient for repeated clinical measurements.<sup>253</sup> DEXA scanning is best performed in all patients with persistently active UC, in those repeatedly exposed to corticosteroids and patients with long disease duration. The presence of osteoporosis identifies patients at above average risk for fracture, who should receive treatment. The presence of osteoporosis is one (but not the only) risk factor for fractures of the spine and peripheral long bones. In recent studies, vertebral fractures have been documented in patients with both reduced and normal bone density; challenging the concept that osteoporosis is the main risk factor for vertebral fractures in young patients with IBD.<sup>254–256</sup> The strongest predictor of future fracture is a prior vertebral fracture. There is, therefore, a need

for prospective studies in young and premenopausal IBD patients to establish a valid assessment tool like the FRAX index used for postmenopausal women.<sup>257,258</sup>

#### Statement 11D

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 and vitamin D should be recommended [EL4, RG C]. Pre-existing history of fracture is of substantial adverse prognostic significance and patients should be treated for osteoporosis even if the *T* score is normal [EL4, RG C]

Treatment with calcium 500–100 mg/day and vitamin D (800–1000 IU/day) increases bone density in patients with IBD.<sup>252</sup> The value of calcium and vitamin D in preventing fractures has not been demonstrated in patients with IBD, although there is value in postmenopausal or steroid-induced osteoporosis.<sup>259</sup> Various bisphosphonates increase bone density in patients with UC (for review see INS; Ref. <sup>252</sup>). Fracture prevention with bisphosphonates has been clearly established in postmenopausal women and steroid-induced osteoporosis but not in young, premenopausal patients with UC. Therefore a general recommendation of treatment with bisphosphonates on the basis of reduced bone density is not feasible. In individual patients with low bone density and additional risk factors treatment should be considered.

#### Statement 11E

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) [EL 2b, 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 [EL3 b, RG C]. Newer data also support the use of strontium salts [EL2a, RG B]. Patients receiving systemic steroid therapy should receive calcium and vitamin D for prophylaxis [EL5, RG D]

Patient's with persistently active disease should be treated according to guidelines with immunosuppressive therapy (azathioprine, TNF $\alpha$  antibodies) to avoid prolonged steroid treatment and general inflammatory activity. It has been shown that a significant proportion of patients with IBD are able to normalise their bone density after 3 years in stable remission.<sup>260</sup> Newer drugs like teriparatide, strontium

relate or recombinant OPG should be prospectively studied in patients with UC before their use can be recommended.

#### 11.4. Cutaneous manifestations

##### Statement 11F

Diagnosis of the cutaneous manifestations of IBD is made on clinical grounds, based on their characteristic features and (to some extent) the exclusion of other specific skin disorders; biopsy can be helpful in atypical cases [EL3b, RG C]

##### Statement 11G

Treatment of erythema nodosum is usually based on that of the underlying Ulcerative Colitis. Systemic steroids are usually required [EL4, RG D]. Pyoderma gangrenosum is initially treated with systemic steroids, topical or oral calcineurin inhibitors [EL4, RG D], infliximab [EL1b, RG C] or adalimumab [EL3b, RG C]

##### 11.4.1. Erythema nodosum (EN)

EN is readily recognised and characterised by raised, tender, red or violet subcutaneous nodules of 1–5 cm in diameter. It commonly affects the extensor surfaces of the extremities, particularly the anterior tibial areas and usually occurs at times of UC activity. A firm clinical diagnosis can normally be made and biopsy is not usually appropriate. If performed, the histology reveals a non-specific focal panniculitis.<sup>261,262</sup> The prevalence of EN in IBD ranges from 4.2–7.5%<sup>221,263,264</sup> and seems to be higher in CD than in UC.<sup>264</sup> The differential diagnosis includes metastatic CD, which may appear at any site as solitary or multiple nodules, plaques, ulcers, or violaceous perifollicular papules, the histology of which includes non-caseating granulomas.<sup>265</sup> Because EN is closely related to disease activity despite a genetic link,<sup>266</sup> treatment is based on that of the underlying UC. Systemic steroids are usually required. In resistant cases or when there are frequent relapses, immunomodulation with azathioprine, infliximab or adalimumab may be used.<sup>267,268</sup>

##### 11.4.2. Pyoderma gangrenosum (PG)

Lesions are often preceded by trauma at the site through a phenomenon known as pathergy.<sup>269</sup> PG can occur anywhere on the body, including the genitalia, but the commonest sites are on 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 wound infection has occurred. In recent publications 0.6–2.1% of UC patients developed

PG.<sup>263,264,270</sup> PG may parallel the activity of the underlying UC or run a course that is independent of it. PG is a diagnosis of exclusion and might be misdiagnosed in a substantial percentage of cases.<sup>271</sup> Histopathological findings in PG are non-specific, but biopsy can be helpful to exclude other specific skin disorders.

Rapid healing should be the therapeutic goal, because PG can be a debilitating skin disorder. There is no evidence that the efficacy of treatment strategies for PG differs between IBD and non-IBD patients. Immunosuppression is the mainstay of treatment. Traditionally the most commonly used drugs with the best clinical experience were systemic corticosteroids and ciclosporin. Corticosteroids have been considered first line treatment, with intravenous ciclosporin and oral and intravenous tacrolimus reserved for refractory cases.<sup>272–275</sup> Infliximab has, however, changed the management of PG in patients with UC. Its effectiveness was first reported in small case studies.<sup>276</sup> The largest study on the treatment of PG with IFX was a multicentre, randomised, placebo-controlled trial of 30 patients, including 19 patients with IBD.<sup>277</sup> IFX 5 mg/kg or placebo was given at week 0. At week 2 (the primary end point), significantly more patients in the IFX group had improved compared to placebo (46% vs. 6%,  $p=0.025$ ). At week 2, subjects in both arms were then offered open-label IFX. Overall, 29 patients received IFX with the majority of them demonstrating a beneficial clinical response: response 69%, remission 31% at week 6. The response rate was over 90% in patients with short duration of PG (<12 weeks) and less than 50% in those with disease present for more than 3 months. Until now, no trial has compared the efficacy of different immunosuppressive drugs. IFX should be considered if a rapid response to corticosteroids cannot be achieved. In patients with peristomal PG, closure of the stoma might lead to resolution of the PG lesions.<sup>278</sup> Topical tacrolimus is an alternative, but specialist advice is recommended.

##### 11.4.3. Sweet's syndrome

Sweet's syndrome is characterised by tender, red inflammatory nodules or papules, usually affecting the upper limbs, face or neck.<sup>279</sup> It has only been recognised as an extraintestinal manifestation of IBD relatively recently.<sup>280,281</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 and patients with colonic involvement and other extraintestinal manifestations. The rash is mostly associated with active disease. Systemic corticosteroids have been reported to be effective.

##### 11.4.4. Anti-TNF-induced skin inflammation

##### Statement 11H

Anti-TNF treatment can induce paradoxical inflammation of the skin [EL4] which is a class-drug effect and is usually reversible upon drug cessation [EL4]. When diagnosis is uncertain, referral to a dermatologist for expert opinion is recommended [EL5 RG D]. Treatment is based

almost entirely on extrapolation from paradoxical skin inflammation in other chronic diseases and it may include topical steroid therapy, topical keratolytic agents, vitamin D analogues, methotrexate, switching anti-TNF or anti-TNF discontinuation [EL3b RGC]

Several centres have reported the development of psoriatic and eczematous lesions in patients with CD and UC receiving anti-TNF therapy, an observation which did not seem to relate to the age of the patient or the duration of treatment.<sup>282</sup> Several isolated case reports have been described, and controlled case-series have been published.<sup>282,283</sup>

Skin lesions are reported in approximately 22% of patients treated on anti-TNF therapy. Psoriasiform eczema, eczema and xerosis were the most commonly observed type of skin lesions and anti-neutrophilic antibodies (ANA) were positively associated with skin paradoxical inflammation.<sup>284</sup>

In a French collaborative study, Rahier et al. assessed clinical characteristics, risk factors, and outcomes of skin disease in patients with inflammatory bowel diseases that presented with psoriatic and eczematous lesions induced by anti-TNF- $\alpha$  agents.<sup>283</sup> A total of 85 patients including CD and UC that developed psoriatic (62 patients) and eczematous lesions (23 lesions) were studied. Locations of eczematous lesions varied whereas scalp and flexural varieties were mostly psoriatic. Skin lesions were not associated with IBD activity, but were more frequent among females and occurred with any type of anti-TNF- $\alpha$  agent (infliximab, adalimumab or certolizumab). Topical therapy with corticosteroids, keratolytics (salicylic acid, urea), emollients, vitamin D analogues and ultraviolet (UV) therapy (UVA or narrow band UVB) resulted in partial or total remission in almost 50% of patients. Patients with psoriatic lesions that did not improve with topical therapy and that switched anti-TNF- $\alpha$  therapies occasionally developed recurrent lesions, suggesting class effect. Overall, 34% of patients had to discontinue anti TNF agents due to uncontrolled skin lesions.<sup>283</sup> The largest case series, however, is derived from the rheumatological literature, and the treatment is mainly based on expert opinion.<sup>285,286</sup>

### 11.5. Ocular manifestations

#### Statement 11I

Patients with ocular manifestations should be referred to an ophthalmologist [EL5, RG D]. Episcleritis may not require systemic treatment and will usually respond to topical steroids or NSAID [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 including anti TNF may be helpful in resistant cases [EL4, RG D]

Uveitis and episcleritis are the most common ocular manifestations of IBD. Episcleritis may be painless, presenting

simply with hyperaemic sclera and conjunctiva, but itching and a burning sensation may also occur.<sup>287</sup> Episcleritis may be self-limiting but will usually respond to topical steroids or NSAID, simple analgesics alongside the treatment of the underlying UC.<sup>287</sup>

Uveitis is less common but has potentially more severe consequences. When related to UC it is frequently bilateral, insidious in onset and long-lasting.<sup>287</sup> Patients complain of eye pain, blurred vision, photophobia and headaches. The possibility of progression to loss of vision should prompt urgent referral to an ophthalmologist. Slit-lamp examination will confirm the diagnosis and permit the differentiation between anterior and posterior uveitis. The treatment will usually consist of both topical and systemic steroids.<sup>287</sup> Azathioprine, methotrexate, infliximab and adalimumab have each been reported to be valuable in resistant cases.

### 11.6. Hepatobiliary disease

#### Statement 11J

Diagnosis of hepatobiliary disorders in association with ulcerative colitis follows the standard investigatory pathways prompted by abnormal liver function tests, with ultrasound scanning, and serology to identify specific auto-immune and infective causes [EL2a, RG B]. Magnetic resonance cholangiography is now established as the first-line diagnostic test for primary sclerosing cholangitis [EL2a, RG B]. Primary sclerosing cholangitis substantially increases the risk of both cholangiocarcinoma and colorectal carcinoma [EL1a, RG A]

Liver test abnormalities are common in IBD and are associated with a small but significant reduction in survival.<sup>288</sup> Primary sclerosing cholangitis (PSC) constitutes the most important condition relatively specific to the underlying IBD. However, pericholangitis, steatosis, chronic hepatitis, cirrhosis, and gallstone formation are also over-represented. In addition, many of the drugs used for IBD have the potential to cause hepatotoxicity. In most cases, the condition will be detected by abnormal liver function tests on routine screening rather than symptoms or signs of liver disease. A predominantly obstructive pattern of liver enzymes or the presence of biliary symptoms will prompt ultrasonographic assessment, which may reveal gall stone disease, steatosis or frank cirrhosis; less often it will show an abnormal duct pattern suggestive of PSC. If ultrasound scanning is normal, drug side effects have been thought unlikely, and serological tests for other primary liver disease are negative then the probability of PSC is significantly increased. The usual diagnostic test is magnetic resonance cholangiography (MRCP), which will show the characteristic pattern of irregular bile ducts, containing areas of both narrowing and dilatation.<sup>289,290</sup> If MRCP is normal it is safer and probably more often diagnostic (given probable predominant small duct disease) to perform a liver biopsy than diagnostic endoscopic retrograde cholangiography

(ERCP) to confirm PSC.<sup>290,291</sup> PSC is a major risk factor for cholangiocarcinoma and colon cancer.<sup>291</sup>

#### Statement 11K

Ursodeoxycholic acid improves abnormal liver function tests [EL1b, RG B], but not histology and prognosis in PSC. ERCP should be used to treat dominant strictures by dilatation and/or stenting [EL4, RG C]. Advanced liver disease may necessitate transplantation [EL2a, RG B]

Ursodeoxycholic acid (ursodiol) was promptly adopted as a treatment for PSC once it was shown to improve liver enzymes,<sup>292</sup> but it has taken some time for reasonably convincing evidence to emerge supporting true benefit from a 20 mg/kg daily dose in respect of histological progression.<sup>293</sup> However in a recent placebo-controlled study with high dose ursodiol (28–30 mg/kg/day) patients in the ursodiol group had a significantly worse outcome despite improvement of liver function tests.<sup>294</sup> Therefore, ursodiol doses should not exceed 20 mg/kg/day. Ursodiol may reduce the risk of colonic cancer in patients with PSC.<sup>143,295</sup> The benefit of steroid therapy has been examined with conflicting results. Tacrolimus resulted in a rapid decrease in liver enzymes but no histological improvement<sup>296</sup> ERCP may still be needed to confirm the diagnosis of PSC in a few cases, and it remains the procedure of choice to manage dominant biliary strictures.<sup>291</sup> In advanced disease with liver failure there is no alternative to liver transplantation but recurrence of PSC in the transplanted liver occurs in approximately 20% of patients.<sup>297</sup> Because of the higher risk of colorectal cancer, it is generally considered appropriate to perform annual screening colonoscopy from the time of diagnosis.

### 11.7. Venous thromboembolism

#### Statement 11L

The risk of thrombosis and related mortality is doubled in patients with UC compared to controls [EL2, RG C]. In patients at risk for thromboembolism prevention with both mechanical thromboprophylaxis and heparin (LMWH or UFH) should be considered [EL5, RG D]. Treatment of venous thromboembolism in IBD should follow established antithrombotic therapy options [EL 1a, RG A] taking into account the potentially increased risk of bleeding [EL5, RG D]

Patients with IBD are at increased risk for venous thromboembolism (VTE), which represents an important cause of morbidity and mortality. The prevalence of VTE in IBD ranges between 1.2 and 6.7% in clinical studies.<sup>298–301</sup> A population-based study and a case–control study revealed

that IBD patients have at least a 2-fold greater risk than the general population and control subjects, respectively.<sup>299,302,303</sup> Furthermore, the risk of recurrence is increased in IBD patients in comparison with non-IBD patients.<sup>304</sup> Deep venous thromboses (DVT) of the leg and pulmonary emboli (PE) are the most common thromboembolic manifestations, but unusual sites of VTE, such as cerebrovascular, portal, mesenteric and retinal veins have also been described. The reason for the increased risk is not completely understood. Acquired risk factors appear to be most relevant and many of the haemostatic alterations parallel inflammatory activity.<sup>301</sup> Thus, the majority of VTE occurs during the active phase of IBD.<sup>299</sup>

The diagnosis of VTE is not considered in further detail and should follow international guidelines<sup>305,306</sup> based on appropriate imaging techniques. The most widely used procedures are ultrasound and venography for diagnosis of DVT and ventilation-perfusion scan and multidetector helical computer axial tomography for diagnosis of PE.

The mainstay of therapy of acute DVT and PE is anticoagulation and should follow international guidelines.<sup>307,308</sup> The benefit of anticoagulant treatment is independent of the diagnosis of UC. In patients with acute DVT and/or PE anticoagulant therapy should be continued, if possible, for at least 3 months using low-molecular-weight heparin, unfractionated heparin or fondaparinux for initial treatment followed by vitamin K antagonists. Long-term treatment should be considered for patients with a second episode of unprovoked venous thromboembolism.

The risk of bleeding complications of IBD patients under anticoagulant therapy compared to non-IBD patients is not known. Major gastrointestinal bleeding may occur, but is rare. A meta-analysis which evaluated the use of heparin for the treatment of UC included 8 randomised-controlled trials.<sup>309</sup> In 6 of 268 patients in the heparin groups an increase in rectal bleeding was reported: only 3 of them had to be withdrawn from the study, including one patient who required urgent surgery. Hospitalisation for an acute medical illness is independently associated with an 8 fold-increased risk for VTE.<sup>310</sup> This risk can be reduced by anticoagulant prophylaxis with low-molecular-weight heparin, unfractionated heparin, or fondaparinux.<sup>310,311</sup> The number of IBD patients included in the studies was too small to draw any sufficient conclusions about the efficacy of anticoagulant prophylaxis specifically in IBD.<sup>312,313</sup> However, hospitalised IBD patients have a higher rate of VTE than non-IBD hospitalised patients, with an associated increased age- and comorbidity-related excess mortality from VTE<sup>298,300</sup> Hospitalised patients with acute severe or fulminant disease are most appropriately treated with anticoagulant prophylaxis with low-molecular-weight heparin, unfractionated heparin, or fondaparinux, especially in the event of prolonged immobilisation.<sup>299,300,311–313</sup> Anticoagulant prophylaxis after abdominal surgery should follow established guidelines.<sup>310</sup> Non-IBD specific risk factors for VTE might further increase the risk. Thus, UC patients should be informed about risk factors for VTE such as oral contraceptive use and long-distance travel.

### 11.8. Cardiopulmonary disease

Cardiac involvement should be considered not only rare, but is usually subclinical. The treatment of IBD-related cardiac



involvement depends on the specific pattern of involvement and patients should be seen by a cardiologist. Pulmonary disease represents the least frequent extraintestinal manifestation of IBD, but it is likely that its true prevalence is unknown. Respiratory symptoms may be present in >50% of IBD patients, but these are often mild, attributed to smoking, or ignored. Drugs, including sulfasalazine, mesalazine and methotrexate may cause a pneumonitis. Respiratory symptoms in patients on anti-TNF therapy should never be ignored, because it may indicate the onset of serious opportunistic infection. The treatment of IBD-related respiratory disease depends on the specific pattern of involvement. Colonic surgery may aggravate prior airway disease.

## 11.9. Anaemia

### 11.9.1. Introduction

The subject of anaemia has previously received little attention,<sup>314</sup> and was not covered as a separate issue in the first edition of these guidelines. However, anaemia is the most common extraintestinal manifestation of IBD. It is not always easy to obtain specific data on UC, but recent epidemiological data confirm that anaemia occurs frequently in both CD and UC.<sup>315</sup> Anaemia is particularly common in severe disease, affecting 66% of all inpatients<sup>316</sup> and 40% of patients in referral centres.<sup>315</sup> Iron deficiency is more prevalent than anaemia, being present in up to 45% of IBD patients.<sup>316,317</sup>

Anaemia is a very relevant clinical condition that may affect quality of life or the ability to work.<sup>318</sup> Furthermore, it can be associated with severe co-morbidities such as transfusion-associated hepatitis C, postsurgical complications<sup>319</sup> or even risk of death.<sup>320</sup> Most of these facts have been fully recognised only in recent years,<sup>316</sup> and an international group of experts has developed guidelines.<sup>321</sup> And there are other reviews for the reader looking for more detail.<sup>322,323</sup>

In UC, the two most important factors are iron deficiency and active inflammation, while haemolytic anaemia and drug-induced anaemia are more uncommon.<sup>322</sup> Iron deficiency anaemia (IDA) may result from chronic blood loss, reduced iron intake or absorption, the anaemia of chronic disease (ACD, also known as anaemia of inflammation) and anaemia of mixed origin (AMO). Although uncommon, vitamin B<sub>12</sub> or folate deficiency and drug-induced anaemia (sulfasalazine, thiopurines, methotrexate, calcineurin inhibitors) should also be born in mind. Determination of the causal factors is not only of academic interest: effective treatment is possible only if the contributing factors in a particular patient are clearly defined.<sup>316</sup>

#### Statement 11M

Anaemia is defined according to the WHO criteria [EL5, RGD]. The major forms of anaemia in ulcerative colitis are iron-deficient anaemia, anaemia of chronic disease and anaemia of mixed origin [EL5, RG D]

Anaemia is defined by the WHO as a decline in blood haemoglobin to a concentration of <12 g/dL (120 g/L) in

women and <13 g/dL (130 g/L) in men. These parameters can equally be applied to patients with ulcerative colitis. However, when determining anaemia purely on the basis of haemoglobin levels, it is important to take account of pregnancy, altitude, cigarette smoking, and possibly ethnicity.<sup>324</sup> Therefore, the WHO has defined differentiated international cutoff values of haemoglobin and haematocrit.<sup>321</sup>

Full evaluation of a patient should include not only haemoglobin, but also haematological values, iron status, vitamin B<sub>12</sub> and folic acid levels, and inflammation markers.<sup>321</sup>

### 11.9.2. Diagnosis of iron deficiency

#### Statement 11N

Diagnostic criteria for iron deficiency depend on the level of colonic inflammation. In patients without any evidence of inflammation a serum ferritin level <30 mcg/L or transferrin saturation <16% define iron deficiency. In the presence of inflammation, the lower limit of serum ferritin consistent with normal iron stores is 100 mcg/L [EL2, RG B]. In the presence of biochemical or clinical evidence of inflammation, the diagnostic criteria for anaemia of chronic disease (ACD) are a serum ferritin >100 mcg/L and transferrin saturation <16%. If the serum ferritin level is between 30 mcg/L and <100 mcg/L a combination of true iron deficiency and ACD is likely [EL 2, RG B]

Normally, low mean cell volume (MCV) and low mean corpuscular haemoglobin (MCH) are reliable parameters of iron deficiency. However, in UC a normal MCV does not exclude iron deficiency as the cause of anaemia, as patients treated with azathioprine or 6-mercaptopurine may have normal or even elevated MCV. Conversely, low MCV does not necessarily imply iron deficiency, because in the presence of ACD it can be normal or low.<sup>317,325</sup> The accuracy of diagnosis for IDA can be improved substantially by including iron metabolism parameters.<sup>317,326</sup>

Isolated iron deficiency, in the absence of inflammation, is usually indicated by the combination of low iron, low ferritin and low transferrin saturation (TfS) with increased transferrin receptor concentrations (sTfR). However, the diagnosis of iron deficiency may also be complicated in UC by the fact that, in this context, iron deficiency and the anaemia of chronic disease frequently coexist and interact in a complex manner,<sup>326</sup> so that a reliable differentiation using these laboratory methods may be impossible.<sup>323</sup> In order to determine the exact type of anaemia in any specific clinical scenario, a combination of parameters should be assessed.<sup>323</sup>

In the absence of biochemical (elevated CRP, leukocytosis) or clinical inflammation, ferritin is a reliable indicator of iron storage levels. A serum ferritin level <15 µg/L indicates absolute iron deficiency.<sup>321</sup> A TfS level below 16% is also a sensitive marker of iron deficiency, though it has a low specificity of only 40–50%.<sup>327</sup>

However, as ferritin, like transferrin, is affected by the acute-phase reaction, an increase in serum ferritin levels can occur in the course of inflammatory processes, suggesting normal iron status in patients who actually have iron deficiency. Therefore, measurements of inflammatory parameters that are independent of iron metabolism (ESR, CRP) should be carried out to aid diagnosis.<sup>321,323</sup>

In the presence of biochemical evidence of inflammation, the lower limit of ferritin consistent with normal iron stores should therefore be increased to 100 µg/L, and hypoferraemia should be considered likely if TfS is <16% and serum ferritin is between 30 and 100 g/L. ACD is likely if serum ferritin is >100 µg/L and TfS is <16%.<sup>321,323,328</sup>

If available, the determination of sTfR (high in iron deficiency, normal or low in ACD) can help to make a correct diagnosis.<sup>328</sup> The haemoglobin concentration in reticulocytes has been suggested as a more exact indicator of iron stores in the context of inflammation, and could also be useful in monitoring response to therapy, although direct experience in IBD is limited.<sup>323,329</sup> The main message for the clinician is that the evaluation of anaemia in any given patient is always incomplete if the inflammatory status is not clearly defined.

### 11.9.3. Treatment of anaemia and iron deficiency

#### Statement 110

Treatment should be considered for all patients with a haemoglobin level below normal. The approach to treatment depends mainly on symptoms, the severity of anaemia and aetiology [EL4, RG D]

Chronic inflammation is frequently a key issue leading to the development of anaemia in patients with UC, and the likelihood of anaemia increases with the severity of the colitis.<sup>316</sup> Treating the underlying UC is therefore the first step in the treatment of anaemia. However, this alone is rarely sufficient to normalise haemoglobin levels and in real clinical practice there is clear evidence that anaemia is often undertreated.<sup>315,321</sup>

As previously stated, anaemia has a profound effect on the quality of life. Normalisation of the haemoglobin level is therefore an objective and auditable goal of the treatment of UC.<sup>316,321</sup> In clinical practice, recurrence of anaemia is common (>50% after 1 year), and is often indicative of ongoing intestinal inflammation.<sup>330</sup> Long-term monitoring of patients successfully treated for anaemia appears warranted in order to detect and treat those with recurrent anaemia. Therefore UC patients in remission, and those with mild disease, should be monitored every 12 and 6 months respectively.<sup>321</sup> Vitamin B<sub>12</sub> and folate levels should be checked at least annually, or if macrocytosis is present.<sup>321</sup>

#### Statement 11P

Iron supplementation should be initiated when iron deficiency anaemia is present [EL1, RG A] and

considered when there is iron deficiency without anaemia [EL4, RG D]. Intravenous iron is more effective and better tolerated than oral iron supplements [EL1, RG A]. Absolute indications for intravenous iron include severe anaemia (haemoglobin <10.0 g/dL), and intolerance or inadequate response to oral iron [EL1a, RG A]. Intravenous iron should be considered in combination with an erythropoietic agent in selected cases where a rapid response is required [EL5, RG D]

If anaemia is present and iron deficiency is proven, iron supplementation should be commenced.<sup>331</sup> In cases of iron deficiency without anaemia, an individualised approach is required. The main goal of therapy for IDA is to supply sufficient iron to increase haemoglobin levels by >2 g/dL or increase them to normal values within 4 weeks, to replenish iron stores (transferrin saturation >30%), to relieve anaemia-related symptoms, and to improve quality of life. Transferrin saturation levels >50% and ferritin levels >800 g/L are considered toxic and should be avoided.<sup>321</sup>

In current practice, the Ganzoni Formula (iron deficit [mg]=body weight [kg]×(target Hb–actual Hb [g/dL]×2.4)+stored iron (500 mg)) is used to calculate individual iron requirement.<sup>332</sup> However, this formula is inconvenient, error-prone, inconsistently used in clinical practice, and almost certainly underestimates iron requirements in IBD.<sup>333</sup>

Iron supplementation can be administered orally, intramuscularly or intravenously. The choice of supplementation method is determined by the symptoms, aetiology and severity of the condition, the dynamics of the haemoglobin decrease, co-morbidities and risks of therapy.<sup>321,323</sup> For many years, oral iron supplementation has been the preferred therapy. The use of intravenous iron preparations has been considered a last resort due to safety concerns.<sup>334</sup> Some patients may respond to oral iron. A very detailed observational study has demonstrated that patients with mild anaemia (Hb >10 g/dL) can be adequately treated according to current guidelines<sup>321</sup> with 100 mg/day iron sulphate.<sup>335</sup> However, as more than 90% of ingested iron remains unabsorbed, oral iron preparations frequently lead to the occurrence of gastrointestinal adverse effects, including nausea, flatulence, diarrhoea and gastric erosion. Moreover, animal and human studies indicate that the generation of reactive oxygen species (Fenton reaction) by non-absorbed iron can potentially lead to the exacerbation of IBD.<sup>335–339</sup> On the other hand, intramuscular iron supplementation should be avoided,<sup>323</sup> since there is no clear clinical evidence demonstrating it to be less toxic or more effective than oral or intravenous iron.

In recent years, several safe IV iron preparations have become available and have become the standard of care for iron replacement in some circumstances in the fields of nephrology and oncology.<sup>334,340,341</sup>

Despite a number of observational and controlled studies in UC and CD demonstrating that IV iron is not only clinically effective but also safe, gastroenterologists still seem hesitant to administer iron intravenously.<sup>328</sup> Several non-randomised<sup>321</sup> and randomised studies<sup>342–344</sup> have shown that IV iron is at least

as effective as oral iron, delivers faster response rates, and is safer in all but a very few patients who may experience side-effects. Intravenous iron therapy is advisable in the following cases: for iron-deficient patients who are intolerant or unresponsive to oral iron supplementation (i.e., those demonstrating an insufficient increase in serum iron parameters within the first 2 weeks of treatment); for patients with severe anaemia (haemoglobin level <10 g/dL (100 g/L)); for patients with pronounced disease activity; and for patients who are being treated with erythropoiesis-stimulating agents.<sup>323</sup>

#### Statement 11Q

Erythropoietic therapy should be considered, when anaemia does not improve in spite of intravenous iron therapy and control of inflammation [EL 2, RG B]. To optimise the effect of erythropoietic agents treatment should be combined with intravenous iron supplementation [EL 2, RGB]

In some patients, treatment of the underlying IBD in conjunction with iron, folic acid and vitamin B<sub>12</sub> supplementation is insufficient to correct anaemia. In such cases, treatment with erythropoiesis-stimulating agents (ESA) is a valid option.<sup>345</sup> A randomised clinical trial demonstrated that erythropoietin combined with IV iron was effective in correcting anaemia in most patients with IBD, which has been confirmed in other studies.<sup>314,345,346</sup> There are limited data on the exact dose and drug to be used, and in this rapidly changing field, local expertise from haematologists or nephrologists can be helpful.<sup>345</sup> However, individual dosage and therapeutic success are critically dependent not only on the availability of sufficient iron, but also on the level of inflammation activity. Increased erythropoiesis requires additional iron for the production of haem; iron supply is regarded as optimal when the transferrin saturation is calculated to be 30–40% and the serum ferritin concentration amounts to 200–500 mcg/L.<sup>321,323</sup> Therapy with erythropoiesis-stimulating agents should therefore always be combined with intravenous iron administration, as functional iron deficiency can essentially always be expected.<sup>321,323</sup> It should be kept in mind that the use of ESA is a risk factor for thrombosis, an otherwise common complication in IBD and particularly in UC. Extensive experience in oncology and nephrology<sup>347,348</sup> suggests that the therapeutic goal with ESA should therefore be a haemoglobin of 11–13 g/dL. It is not clear whether the same goal can be applied to treatment of anaemia in patients with IBD.

#### Statement 11R

Blood transfusion should be restricted to very special clinical situations, such as acute severe anaemia with hemodynamic instability, severe anaemia-related weakness and fatigue and/or failure of all other treatments [EL 5 RG D]

Red blood cell (RBC) transfusion was rather frequently used in the past. However, even though infectious risks have been greatly reduced,<sup>349</sup> RBC transfusions are still associated with increased risks of venous and arterial thrombotic events,<sup>350</sup> acute and delayed transfusion reactions, and transfusion-induced immunomodulation.<sup>317,349,351</sup> Furthermore, red blood cells are an expensive and scarce resource.<sup>352</sup> Therefore, the use of RBC transfusion should be limited only to certain specific situations: acute anaemia with haemodynamic instability, severe anaemia-related fatigue, and/or failure of other treatments.

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#### Members of working parties for the update 2011/2012:

##### Pouchitis

Paolo Gionchetti (IT), Chair  
Francisco Portela (PT)  
Herbert Tilg (AT)

##### Surveillance for colorectal cancer in UC

Laurent Beaugerie (FR)  
Bernd Bokemeyer (DE), Chair  
Bas Oldenburg (NL)  
Julian Panes (ES)

##### Psychosomatics

Winfried Häusler (DE)  
Gabriele Moser (AT), Chair  
Gerhard Rogler (CH)

##### Extraintestinal manifestation of UC and anaemia

Silvio Danese (IT), Chair  
Fernando Gomollon (ES)  
Klaus Herrlinger (DE)  
Jürgen Michael Stein (DE)

#### The contributors to the consensus were the following:

M. Allez, Hôpital Saint-Louis, Paris, France  
L. Beaugerie, Hôpital Saint-Antoine, Paris, France  
B. Bokemeyer, Gastroenterologische Gemeinschaftspraxis, Minden, Germany  
Y. Chowers, Rambam Health Care Center, Haifa, Israel  
J.-F. Colombel, Hospital Huriez, Lille, France  
S. Danese, Istituto Clinico Humanitas, Rozanno, Milan, Italy  
G. D'Haens, Academic Medical Centre, Amsterdam, The Netherlands  
A. D'Hoore, University Hospital Gasthuisberg, Leuven, Belgium  
A. Dignass, Agaplesion Markus Krankenhaus, Frankfurt, Germany  
R. Eliakim, Sheba Medical Center, Tel Hashomer, Israel  
P. Gionchetti, Università di Bologna, Bologna, Italy

F. Gomollón Garcia, Hospital Clinico Universitario, Zaragoza Spain,  
 W. Häuser, Klinikum Saarbrücken, Saarbrücken Germany  
 K. Herrlinger, Asklepios Klinik Nord – Heidberg, Hamburg, Germany  
 J. Lindsay, Barts and the London NHS Trust, London, United Kingdom  
 C. Maaser, Klinikum Lüneburg, Lüneburg, Germany  
 F. Magro, Sao Joao Hospital, Porto, Portugal  
 G. Mantzaris, Evangelismos Hospital, Athens, Greece  
 G. Moser, University Hospital Vienna, Vienna, Austria  
 G. Novacek, Medical University of Vienna, Vienna, Austria  
 B. Oldenburg, University Medical Centre UMC Utrecht, Utrecht, The Netherlands  
 T. Øresland, Akershus University Hospital, Lorenskog, Norway  
 J. Panes, Hospital Clinic Barcelona, Barcelona, Spain  
 F. Portela, Coimbra University Hospital, Coimbra, Portugal  
 W. Reinisch, University Hospital Vienna, Vienna, Austria  
 G. Rogler, University Hospital Zurich, Zurich, Switzerland  
 M. Sans, Centro Medico Teknon, Barcelona, Spain  
 E. Stange, Robert Bosch Krankenhaus, Stuttgart, Germany  
 J. M. Stein, Crohn Colitis Center, Frankfurt, Germany  
 A. Sturm, Krankenhaus Waldfriede, Berlin, Germany  
 H. Tilg, Bezirkskrankenhaus Hall in Tirol, Hall in Tirol, Austria  
 S. Travis, John Radcliffe Hospital, Oxford, United Kingdom  
 G. van Assche, University Hospital Gasthuisberg, Leuven, Belgium  
 S. Vermeire, University Hospital Gasthuisberg, Leuven, Belgium  
 A. Windsor, University College London Hospital, London, United Kingdom

#### The Contributors to the consensus meeting per country were:

Austria: Moser, Novacek, Reinisch, Tilg  
 Belgium: D'Haens, D'Hoore, Franchimont, van Assche, Vermeire  
 Bulgaria: Kotzev, Spassova  
 Croatia: Cukovic Cavka, Vucelic  
 Czech Republic: Bortlik, Doua  
 Denmark: Dahlerup, Kjeldsen  
 Finland: Färkkilä  
 France: Allez, Beaugier, Carbonnel, Colombel  
 Germany: Bokemeyer, Dignass, Häuser, Herrlinger, Maaser, Stange, Stein, Sturm  
 Greece: Karagiannis, Mantzaris, Tsianos  
 Hungary: Lakatos,  
 Ireland: Egan, O'Morain  
 Israel: Eliakim, Odes  
 Italy: Danese, Gionchetti, Cottone, Kohn  
 Lithuania: Kriukas, Kupcinskas  
 Norway: Berset, Øresland, Jahnsen  
 Poland: Rydzewska  
 Portugal: Magro, Portela  
 Romania: Cijevschi Prelipcean, Diculescu  
 Russia: Belousova, Potapov  
 Serbia: Tarabar  
 Slovakia: Gregus, Huorka  
 Slovenia: Stabuc  
 Spain: Casellas Jorda, Gomollón Garcia, Panes, Sans,

Sweden: Hertervig  
 Switzerland: Rogler, Michetti, Seibold  
 The Netherlands: Fidler, Weersma  
 Turkey: Ferhat Celik, Törüner  
 Ukraine: Dorofeyev, Zviagintseva  
 United Kingdom: Lindsay, Travis, Windsor

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