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REVIEW

Inflammatory bowel disease position statement of the Italian Society of Colorectal Surgery (SICCR): Crohn's disease

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Abstract

The Italian Society of Colorectal Surgery (SICCR) promoted the project reported here, which consists of a position statement of Italian colorectal surgeons to address the surgical aspects of Crohn's disease management. Members of the society were invited to express their opinions on several items proposed by the writing committee, based on evidence available in the literature. The results are presented, focusing on relevant points. The present paper is not an alternative to available guidelines; rather, it offers a snapshot of the attitudes of SICCR surgeons about the surgical treatment of Crohn's disease. The committee was able to identify some points of major disagreement and suggested strategies to improve quality of available data and acceptance of guidelines.

Keywords Inflammatory bowel disease · IBD · Crohn's disease · Strictureplasty · Surgery

Introduction

Surgical management of Crohn's disease (CD) requires expertise and dedicated facilities. In 2015 the Italian Society of Colorectal Surgery (SICCR) conducted a Delphi exercise involving expert Italian members of the society, concerning the surgical management of inflammatory bowel disease [1, 2], and several areas of moderate agreement were identified.

The rapidly evolving Italian regulations concerning the management of patients requiring surgical treatment, with

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formal accreditation of national scientific societies which are in charge of delineating the ideal "diagnostic, therapeutic, and clinical care protocol" (percorso diagnostico terapeutico assistenziale, PDTA in Italian, law 08/03/2017 n 24), led to a renewed attention to guideline-type statements, to be followed in everyday practice. Several international societies have developed guidelines on IBD [3–6] and specifically CD; but the actual applicability might differ in each specific country. The aim of the committee was not to replace the currently available guidelines, rather to stimulate discussion about the surgical issues in IBD among experts at a national level, to shape the treatment to address national needs; and focus attention on the importance of applying management pathways in everyday practice nationwide.

The aim of the current project of the SICCR, was to develop a position statement of Italian surgeons concerning the management of CD. A patient representative was involved in the entire process. This is not intended as strict rules of conduct, but should be interpreted as a decisional aid, to be adapted to each individual patient.

Methods

In April 2019, the SICCR designed the current Delphi project. The chair of the IBD committee of the SICCR and the executive committee selected a steering committee, which included members of the SICCR, a patient representative (SL), an external collaborator (DSK), and an external expert (SD). The project design and timeline were completed by the committee, and experts were identified. Topics and questions were discussed and approved by the steering committee. Individual invitations were sent, and participants were assigned to three working groups: CD; ulcerative colitis; and general principles of management of IBD [7–9]. Each collaborator contributed with a specific section; he/she performed the review of the literature, drafted the statements with evidence levels (EL) graded according to "The Oxford Levels of Evidence 2″ of Oxford Centre for Evidence-Based Medicine OCEBM (https://www.cebm.net/index.aspx?o=5653), along with a brief supporting text. Contributions were collated and circulated via SurveyMonkey (SurveyMonkey Inc., San Mateo, CA, USA, www.surveymonkey.com). The literature included all the articles published until June 2019. Available guidelines were taken into account, and cited in the text.

In July 2019, members were asked to rate the survey items according to a 4-point Likert scale ("Agree"—"Partially agree"—"Neutral"—"Disagree"), and to make any comments they considered important.

Answers were reviewed by the steering committee and the outcome of the voting along with comments was sent back to the authors. Agreement was achieved when 80% or more of the participants approved.

Statements and supporting text about which there was less than 80% agreement were reviewed according to the committee members' comments and resubmitted for a second round of voting in October 2019.

The manuscript was finalized by the steering committee and circulated among collaborators. Agreement was included for each included statement; those about which there was less than 80% agreement were either deleted or moved to the supporting text. Some statements with > 80% agreement were revised to include the comments received.

Small bowel surgery

Endoscopy

Item 1
Ileocolonoscopy with multiple random biopsies is the most reliable tool to detect CD (EL1) Endoscopy in IBD should be performed by an endoscopist with expertise in IBD diagnosis and clinical management (EL5)
[Agreement: "Agree" 94.1%, "Partially agree" 5.9%, round I]

Endoscopy plays an important role both in diagnosis and clinical management of IBD [10]. Endoscopic biopsies should be performed both in normal and inflamed mucosa [11–13]. Preserved crypt architecture and acute inflammation are not typical features of CD [14]. Endoscopy in IBD requires a deep knowledge of the disease because it can be technically challenging and endoscopists must have specific training [15]. The efficacy of ileocolonoscopy is affected by bowel preparation, the quality of which can be evaluated with several scores [10, 16, 17]. Polyethylene glycol (PEG) laxatives in split doses are useful also in intolerant patients or in presence of stenosis, whereas sodium-phosphate based purgatives could produce mucosal changes jeopardizing the diagnosis [10, 18].

Item 2
Capsule endoscopy might be considered to evaluate the small bowel when endoscopic findings are normal (EL2). Bowel preparation is recommended (EL2). The assessment of risk of retention is advisable in case of fibrostenotic disease, when a magnetic resonance(MR)/computed tomography(CT) enterog-

raphy should be performed before capsule endoscopy (EL2)
[Agreement: "Agree" 94.1%, "Neutral" 5.9%, round II]

Small bowel capsule endoscopy (SBCE) is a reliable diagnostic tool in small bowel CD, especially when conventional endoscopy does not detect any mucosal abnormalities or in case the endoscopic access to the small bowel is difficult. SBCE has demonstrated a better sensitivity in detecting small bowel disease when compared with other imaging techniques and when performed by gastroenterologists with specific expertise [19, 20]. Bowel preparation with PEG in any dose or volume (from 1 to maximum 4 l) is advisable [21]. Patients are allowed clear fluids after 2 h and solid food after 4 h. IBD-specific scales such as the Lewis Score and the CD Activity Index should be used to standardize reporting of SBCE findings [20–22]. However, there is a rate of capsule retention in IBD patients of 4–8% which could be reduced with appropriate assessment through imaging technique (MR/CT enterography) prior to SBCE or use of a patency capsule [23, 24]. A patency capsule could be successfully used also in patients with stricturing or penetrating disease phenotypes [25].

Item 3
Ileocolonoscopy is recommended within 6–12 months after ileocolic resection to detect postoperative recurrence (EL2). Alternatively, non-invasive diagnostic modalities, such as intestinal ultrasound(US) or MR enterography can accurately detect recurrence within 6–12 months after surgical resection. SBCE is a valid option but the risk of retention should be minimized with patency capsule evaluation (EL2)
[Agreement: "Agree" 82.35%, "Partially agree" 17.65%, round II]

After ileocolic resection, endoscopic mucosal recurrence has been reported to range between 65–90% within 12 months after surgery [26, 27]. Ileocolonoscopy is recommended within 12 months after ileocolic resection and is the reference standard to detect recurrence and define its severity with the Rutgeerts score. Postoperative recurrence in proximal small bowel could also be assessed with capsule endoscopy. SBCE is equivalent or superior to conventional endoscopy in the evaluation of the Rutgeerts score to detect CD recurrence [28, 29] and has the added advantage of detecting lesions outside the scope of ileocolonoscopy but the drawbacks include requirement of radiologist studies or the use of a patency capsule although this may not be needed early postoperatively or in patients with no obstructive symptoms [30]. Intestinal US and MR enterography have also demonstrated high diagnostic accuracy in detection of endoscopic recurrence after surgery [31].

Balloon dilatation

Item 4
Balloon dilatation could be considered as a non-invasive option for the management of symptomatic short strictures. It needs a high grade of expertise and it is advisable to have surgical back-up during and after the procedure (EL3)
Recurrence of stricture is common and can be treated with repeated dilatation instead of surgery, according to clinical conditions and technical feasibility (EL3)
[Agreement: "Agree" 94.1%, "Partially agree" 5.9%, round II]

Endoscopic balloon dilatation (EBD) is a minimally invasive method to manage symptomatic strictures preserving bowel length. It is indicated in short primary (< 5 cm) and anastomotic strictures [32]. Dilatation of strictures < 5 cm presented a longer surgery-free interval with an increased risk of surgery of 8% with every 1 cm increase in the stricture length. Endoscopic dilatation has an 89% technical success rate, 80.8% clinical efficacy and a complication rate of 2.8% [33]. Re-dilatation is required in 73.5% of cases and surgery in 42.9% of cases within 24 months, with most strictures requiring a mean of 3 dilatations to achieve stable results [34, 35]. Dilatation of de novo strictures has a better success rate than anastomotic strictures but the same long-term outcome [33]. Surgical back-up should be available during and after the endoscopic procedure [36]. EBD can be repeated in case of clinical and endoscopic recurrence with the same efficacy and outcome [37]. Repeated dilatations are not associated with higher risk of complications. In long-standing CD there is increased risk of small bowel malignancy, so prior to dilatation the stricture should be biopsied [34]. There is no evidence that biopsies increase the risk of perforation during the procedure [38].

Item 5
EBD is not contraindicated in presence of inflammation or ulceration (EL3). Both EBD and strictureplasty are contraindicated in the presence of abscess, fistula or suspected malignancy (EL3)
[Agreement: "Agree" 94.1%, "Partially agree" 5.9%, round I]

In a systematic review comprising 1463 patients, the outcome (both short- and long-term) and the complication rate were not affected by inflammation and disease activity. The characteristics of the stricture (location, type, length) and of the balloon (length, diameter, pressure) have no impact on complication rate [33]. No death has ever been reported. Several factors influence outcome after EBD. A single stricture with length < 5 cm without ulceration

and a technically successful procedure are associated with favorable outcomes [39, 40]. Medical treatment after EBD could influence the disease course and, therefore, the outcome of the procedure [37].

Strictureplasty

Item 6
Strictureplasty is indicated for the treatment of either primary or recurrent CD of the small bowel with non-penetrating behavior (EL2)
[Agreement: "Agree" 100%, round I]
Item 7
Short stenotic segments (< 6-8 cm) are best treated with the Heineke-Mikulicz technique. For multiple and close strictures or long segments, the side-to-side, isoperistaltic strictureplasty proposed by Michelassi is the best option (EL2)
[Agreement: "Agree" 64.71%, "Partially agree" 29.41%, "Neutral" 5.88%, round I]

In the literature the Heineke-Mikulicz and the Finney techniques are defined as conventional strictureplasties. Ileo-ileal isoperistaltic strictureplasty, modifications of the conventional strictureplasty for complex stenosis, strictureplasty of the ileocecal region, and strictureplasty of intestinal segments with fistulas are defined as non-conventional strictureplasty. Minimal bowel resection is a resection without the removal of microscopically involved bowel margins (regardless of the length of the small bowel segment). Conservative surgery is a surgical approach based on strictureplasty and minimal bowel resection aimed at maximum bowel preservation [34, 41–60].

Recent reviews and meta-analyses have provided evidence about the use, indications, techniques, complications and long-term results of both conventional and non-conventional strictureplasty [43, 59, 60]. The mortality was nil, and the overall complication rate ranged from 5 to 20%. Small bowel obstruction (2.6%), leaks (4.2%), bleeding (3.2%), and reoperation (2.8%) were the most common complications. The èong-term recurrence rate was 25–70% at 10 years depending on patient characteristics. Interestingly, more than 50% of the patients included in the meta-analysis of Campbell et al. underwent strictureplasty as the first surgical procedure, and not for recurrent disease, or salvage surgery in short bowel syndrome as previously reported [61]. Ninety percent of conventional strictureplasty are Heineke-Mikulicz, while 80% of non-conventional strictureplasty are ileo-ileal, isoperistaltic, side-to-side strictureplasty, as proposed by Michelassi [42, 45, 51, 61, 62]. The most intriguing aspect of strictureplasty is the apparent return to normality of the bowel and the very low site-specific recurrence rate, which has been reported to be 2–5% at 10 years [42, 45, 51, 61, 62].

Resection

Item 8
Patients with localized CD with symptoms of obstruction with no evidence of active inflammation, are best treated with surgery (EL2)
[Agreement: "Agree" 94.12%, "Partially Agree" 5.9%, round I]

Adapted from the 2018 ECCO-ESCP consensus on surgery for CD [32]. It is important to have determined and documented the exact number, length, and features of all the lesions of the small intestine before embarking on surgery [63]. After intraoperative identification of the number, the locations, and the characteristics of the small bowel CD lesions, the treatment should be customized 'per segment' on the basis of the characteristics of each single lesion. The role of SP techniques for short strictures or multilevel and recurrent disease is discussed in statements 6 and 7. It is advisable to measure the intestinal length before and after resection [64].

The LIR!C study also demonstrated the value of laparoscopic surgical resection as a reasonable alternative to infliximab therapy in patients with limited (diseased terminal ileum < 40 cm), non-stricturing CD not responding to conventional medical treatment [65]. This was a RCT conducted in 29 teaching hospitals in the Netherlands and UK, in which adult patients with non-stricturing ileocecal CD were randomized 1:1 to receive either laparoscopic ileocecal resection ($n = 73$) or infliximab ($n = 70$). Surgical complications classified as IIIa or worse on the Clavien–Dindo scale occurred in four patients in the resection group, whereas two patients in the infliximab group had treatment-related serious adverse events. During a median follow-up of 4 years, 26 (37%) patients in the infliximab group had resection, and 19 (26%) in the resection group received anti-TNF.

Item 9
In the event of symptomatic abdominal fistulae (enterourinary, fistulae with bowel stricture and/or abscess, malabsorption), surgery is recommended. (EL 2)
[Agreement: "Agree" 100%, round I]

Adapted from the 2018 ECCO-ESCP consensus on surgery for CD [32]. CD fistulae require surgery because of the risk of severe malabsorption or fecal contamination of the upper gastrointestinal tract, and the potential of severe urinary and biliary sepsis [66, 67]. Despite the diverse spectrum of the various fistulae, their surgical repair rests on common principles: transection of the fistulous tract, drainage of any

intervening abscess, resection (or rarely SP) of the diseased segment, and primary closure of the fistulous opening on the target organ, after appropriate debridement [68]. If the target organ is another segment of intestine and the defect is large or is located on the mesenteric side or is associated with a substantial inflammatory reaction, the affected segment of intestine may require a limited resection [69].

Item 10
In case of penetrating ileocecal disease with fistula formation, resection is recommended. Penetrating CD presenting with intra-abdominal abscess should be treated by percutaneous drainage where possible, followed by patient optimization and elective surgical resection in the majority of cases. (EL3).
[Agreement: "Agree" 100%, round II]

Penetrating disease with enteric fistula formation represents an indication for resection; data show how any delay to surgery, once the patient starts to clinically deteriorate, with sequential attempts of conservative treatments, is associated with larger inflammatory masses, weight loss, and a higher postoperative morbidity [70]. The only exceptions may be the rare cases in which entero-enteric fistulas are not associated with strictures or abscesses and do not bypass long bowel segments, thus not creating diarrhea or malabsorption [5]. If an abscess is present, patient optimization with abscess resolution is advocated to reduce the risk of anastomotic leak or staged procedures with stoma formation. When abscesses are smaller than 3 cm, antibiotic therapy with close clinical observation may be attempted despite a high recurrence rate [71–73]. If abdominal abscesses are larger than 3–5 cm percutaneous US- or CT-guided drainage is indicated, with a short-term success rate of up to 50%, as regards avoiding surgery within 60 days and reduction of stoma formation [74]. Many studies have also demonstrated the advantages of percutaneous vs surgical drainage in terms of lower morbidity, reduced overall length of bowel resected, reduced stoma creation rate, and shorter hospital stay [75–78], with the opportunity of patient optimization before definitive surgery, including nutritional support and weaning off steroids [79]. Percutaneous abscess drainage and control of sepsis may prevent an urgent operation and allow for improvement of the patient's overall condition prior to semi-elective surgery [80]. Abdominal abscesses can be drained percutaneously under US or CT guidance [74]. A meta-analysis of five studies including 108 patients undergoing attempted definitive percutaneous drainage found that 43 patients eventually had surgery [78].

After drainage, a waiting period of 6–8 weeks is suggested to obtain a better stabilization of the patient's condition, with significant decrease of postoperative septic complications [81]. The role of biologics in patients with luminal CD, complicated by intra-abdominal abscess after complete resolution of infection is currently being investigated by the ongoing "MICA study" from the GETAID group.

Surgical technique (approach/anastomosis)

Item 11
When surgery is indicated, laparoscopic resection has to be considered as the preferred approach for primary ileocecal disease (EL1)
[Agreement: "Agree" 100%, round II]
Item 12
In expert hands, laparoscopic surgery may be attempted in complex, fistulising, and recurrent disease (EL2)
[Agreement: "Agree" 94.12%, "Partially agree" 5.9%, round II]

It has been clearly demonstrated that laparoscopic surgery confers short-term benefits in the setting of CD, in terms of better cosmesis, shorter return to bowel functions, shorter hospital stay, earlier recovery and reduced wound complications. Additional benefits might include less intrabdominal septic complications and blood loss. The safety and benefits of laparoscopic surgery, together with long-term results not inferior to those achieved with open surgery, even in terms of disease recurrence, have been demonstrated both in randomized trials and meta-analysis [82–86]. Short-term benefits of laparoscopic surgery might potentially be further improved within a well-established enhanced recovery program, with even earlier return to bowel function and shorter hospital stay [87].

The reoperation rate for adhesions or incisional hernia seems to be lower after laparoscopic surgery, as was demonstrated by a US nationwide registry study on 49.609 resections for CD, which also showed lower overall morbidity (8% vs 16%) and mortality (0.2 vs 0.9%) rates [88].

Despite such advantages, laparoscopic surgery for CD is still underutilized [88]. Most likely because surgery for complex and recurrent disease is technically challenging. Current data have demonstrated its safety in expert hands. Patients can benefit from laparoscopic surgery even taking into account the risk for a higher conversion rate that seems to be related to disease severity (number of acute flares), preoperative immunosuppressive therapy, and intra-abdominal abscesses or fistulas [89–92].

No agreement was reached concerning a statement on the type of anastomosis to use for these patients.The role of anastomosis configuration in the reduction of anastomotic recurrence and postoperative morbidity has been investigated in several prospective studies [93–97], trials, and meta-analyses. At least three meta-analysis have demonstrated that a wide lumen stapled side-to-side (functional end-to-end) ileocolic anastomosis, is associated with a

significantly reduced leak rate [98, 99].A third meta-analysis has also showed a reduction in recurrence and reoperation rate [100]. Nevertheless, this meta-analysis includes both randomized and non-randomized studies and when only randomized trials are considered, including ileocolic anastomosis for CD, no anastomotic configuration has been shown to be superior in terms of preventing recurrence. An even more recent network meta-analysis [101] concluded that a stapled side-to-side anastomosis is superior in terms of lower leak rate, but also in preventing endoscopic recurrence and reoperation rate at the anastomotic site; but, of the 11 studies included, only four were prospective randomized studies and more than half of the studies were retrospective; moreover, the significant heterogeneity among studies is a further risk of bias. Therefore, the theoretical indication to perform a stapled side-to-side anastomosis should be only based on a potential reduction of postoperative leak rate, which has not been demonstrated in all the studies.

A novel anastomotic configuration, the Kono-S anastomosis, was described in 2011, with the aim of reducing endoscopic and surgical recurrence in CD [102]. It is a combined stapled and handsewn anastomosis (functional end-to-end), entirely realized at the anti-mesenteric side of the bowel. The latter is supposed to be one of the main mechanisms of the Kono-S anastomosis in preventing recurrence, which always appears at the mesenteric side of the bowel, completely excluded from the anastomosis lumen. Recently, a comparative, non-randomized study by Shimada et al. [103], has demonstrated that, when compared with end-to-end anastomosis, Kono-S anastomosis is both useful in preventing surgical recurrence and reducing the leak rate. However, the role of this anastomosis needs to be further elucidated and at least two prospective randomized trials to better assess the role of the Kono-S anastomosis in CD are currently ongoing [104, 105].

Ileocecal disease

Indication for surgery

Item 14
Acute setting
Perforation is a rare and acute indication for surgery. Bowel resection is the treatment of choice and primary anastomosis is reserved for selected cases (EL4). Patients with obstruction, abscesses, and hemorrhage should undergo surgery in case of failure of conservative treatment (EL4).
[Agreement: "Agree" 87.50%, "Partially Agree" 6.25%, "Disagree 6.25%, round I]

CD requires emergency surgery in 6–16% of cases. Free perforation of the small bowel affects 2% of patients and requires urgent surgery. Resection of the perforated loop is preferred over simple suture because of the high postoperative mortality and morbidity rates. Perforations with diffuse peritonitis, poor condition of adjacent bowel loops, dilatation and/or edema, and cases of technical difficulties in constructing the anastomosis, should be managed with bowel resection and end or diverting stoma. The primary anastomosis should be performed in absence of fecal peritonitis or intestinal distress in hemodynamically stable patients with no comorbidities [106].

Acute intestinal obstruction, due to inflammatory strictures, often responds to conservative management. Conservative treatment may relieve symptoms allowing radiological re-evaluation [107] and improvement of nutritional and immunological status in preparation for elective surgery. A cohort study conducted on 10,913 IBD patients showed that preoperative hypoalbuminemia was associated with more 30-day postoperative mortality and severe complications [108]. In cases of persistent symptomatic strictures or peritoneal irritation or suspected bowel ischemia urgent surgery is mandatory [32].

Abscesses in CD should be treated with antibiotics and percutaneous drainage (PD). Drainage is discussed in Statement 10.

Massive digestive tract bleeding is an uncommon complication. Surgery is indicated only in case of failure of conservative treatment with endoscopic and/or interventional radiological techniques [109].

Every effort should be made to optimize patients ahead of surgery, and a strict collaboration between gastroenterologists and surgeons could reduce the number of patients with CD who need surgery in emergency settings, as this is associated with more extended resections and higher stoma formation rates [110].

Item 15
Elective setting
Surgery is recommended either in patients with disease not adequately controlled by medical therapy or non-compliant with medical treatment (for side effects or contraindications) (EL4)
[Agreement: "Agree" 87.50%, "Partially Agree" 6.25%, "Disagree" 6.25%, round I]

Patients with symptoms of active inflammation should be first treated by medical therapy [32]. Medical therapy is associated with various side effects such as acute infusion reactions, drug-induced immunological diseases, neurological complications [111], and a slightly increased risk for lymphoma [112]. Both corticosteroids and anti-tumor necrosis factor alpha (anti-TNF alpha) are linked with a significantly increased risk of osteoporosis [113]. When major side

effects occur or if there are relative or absolute contraindications to medical therapy (e.g. active or previous malignancy or latent infectious disease) surgery is recommended [111].

Some patients experience primary or secondary refractoriness (resulting from a loss of response) towards medical therapy, or their disease cannot be controlled with drugs other than steroids (steroids dependence).Surgery is the only therapeutic option in these patients [4].

After failure of conventional medical therapy for limited, non-stricturing, ileocecal CD, some authors have proposed a minimally invasive laparoscopic resection as a possible alternative to anti-TNF alpha therapy [65], but evidence on this topic is still limited.

Once the need for surgery is established, surgery should not be delayed, as long-term results could be impaired [114].

Item 16
Elective setting
Patients with symptomatic fibrostenotic strictures confirmed by CT or MR enterography should undergo surgery for resection or strictureplasty as well as symptomatic strictures that do not respond to medical therapy. Endoscopic dilation can be suggested for short and accessible strictures with no associated fistulae (EL4). Symptomatic penetrating CD might require early surgery for the high probability of medical treatment failure and the risk of abscesses and sepsis during immunosuppressant therapy (EL4).
[Agreement: "Agree" 87.50%, "Partially Agree" 6.25%, "Disagree" 6.25%, round I]

Strictures complicating CD are classified as mainly inflammatory or fibrostenotic [34, 115, 116]. CT enterography and MR enterography have a relatively high sensitivity and specificity and, in addition to inflammatory markers, are valuable for distinguishing inflammatory from fibrostenotic strictures [117]. Recently, it has been suggested that positron emission tomography (PET)/ magnetic resonance imaging (MRI) can be used to identify the inflammatory component of CD strictures [118, 119]. Patients with obstructive symptoms and minimal inflammatory activity should be considered for early surgery because they will probably have a poor response to medical therapy [3]. Endoscopic dilation of the pathological area can be used for strictures that are readily accessible and shorter than 5 cm [120].

Surgery is also indicated for symptomatic small bowel strictures that do not respond to medical therapy or in the case of failure of conservative techniques such as endoscopic dilation [45].

Patients with penetrating/fistulizing CD and associated symptoms (recurrent infections, malabsorption, and abdominal pain) should undergo surgery due to the higher risk of non-response to medical treatment and the risk of complications such as abscesses [32]. The presence of malabsorption and symptoms from recurrent sepsis should discourage from prolonging medical treatment. Early surgery is a viable option in a subset of CD, and it might mitigate disease course and reduce the likeliness of receiving biologics compared with surgery performed at later stages [121]. Surgery is not indicated in case of entero-enteric fistulas without associated symptoms such as malabsorption or diarrhea (incidental finding at MR or CT enterography) [122].

Strictureplasty

Item 17
Non-penetrating disease of the terminal ileum or a previous ileo-colonostomy can be treated by ileo-colic SP, with safety, efficacy, and long-term recurrence equivalent to resections (EL2). Widening and side-to-side ileocolic SP are the preferred techniques (EL2)
[Agreement: "Agree" 68.75%, "Partially Agree" 12.50%, "Neutral" 12.50%, "Disagree" 6.25%, round I]

The ileocecal region is the most common site of CD presentation, and the surgical recurrence rate in this region is high. Preserving the terminal ileum is an interesting option to be combined with modern biological adjuvant therapy. Whether there is complete restitutio ad integrum of the diseased bowel segment, with normal function, after SP has not yet been proven. However, we have a number of findings, in prospective studies, that shows a normalization of both mucosal and transmural CD alterations. In particular, complete mucosal healing after ileocolic SP can be demonstrated endoscopically. Furthermore, results of SP in terms of safety and efficacy, and long-term recurrence rates are comparable, if not better, than results of resection [32, 41–43, 48, 51, 123–133].

Surgical approach

Item 18
A minimally invasive approach should be the first choice in the surgical treatment of patients with ileocecal CD. (EL1) Laparoscopy can also be an option in case of recurrent or fistulizing CD of the terminal ileum, as long as surgery is performed by expert surgeons (EL3)
[Agreement: "Agree" 87.5%, "Partially Agree" 12.50%, round I]

A minimally invasive approach should be the first choice in patients with primary CD of the terminal ileum. The rate of long-term recurrence after laparoscopic and open resections has been proven to be comparable [134]. After laparoscopic surgery, better short-term outcomes

have been reported. In particular, faster oral intake, shorter time to bowel function, shorter hospital stay, lower overall postoperative complication rates. In the long term, a lower rate of incisional hernias, and improved body image scores after a laparoscopic approach were demonstrated by several single center studies and meta-analyses [83, 85, 86, 135, 136].

Laparoscopy can be safely performed in selected patients with recurrent CD. The rate of postoperative complications is similar to that expected after open surgery, as shown by a recent meta-analysis [137]. A previous laparotomy does not contraindicate a laparoscopic approach [138]. Surgery for recurrence should be performed in expert center, taking into consideration the higher risk of conversion to open surgery [139].

Anastomotic technique

Item 19
After ileocolic resection, a wide lumen, stapled, ileocolic side-to-side anastomosis is the preferred technique. (EL1). Performing circular end-to-end, end-to side, and side-to-side (with double blind stump) anastomosis is strongly discouraged (EL2)
[Agreement: "Agree" 68.75%, "Partially Agree" 12.50%, "Neutral" 12.50%, "Disagree" 6.25%, round I]

First part adapted from 2018 ECCO-ESCP consensus on surgery for CD [32]. When there is an indication for an intestinal resection, there is strong evidence from 2 meta-analyses, one based on eight comparative studies in CD patients and one based on seven radomized controlled trials in colorectal surgery from the Cochrane Database of Systematic Reviews, that a stapled, functional end-to-end anastomosis is associated with a lower leakage and overall postoperative complications rate than hand-sewn end-to-end (but not side-to-side) anastomosis. Manual or stapled end-to-end, end-to-side and side-to-side with double blind stump are associated with a worse long-term recurrence rate, and higher postoperative complication rate. It seems that wide anastomotic diameter is an important discriminating factor, whatever anastomotic technique is used [93–99, 140, 141].

A single-center, randomized, controlled trial compared the 6-month endoscopic recurrence of conventional stapled side-side ileocolic anastomosis versus Kono anastomosis after ileocolic resection for small bowel CD [142]. Seventy-six patients were randomized to receive either conventional ($n=43$) or Kono anastomosis ($n=36$) after ileocecal resection. Kono anastomosis was associated with 22.2% endoscopic recurrence at 6 months, compared with 62.8% in the conventional group ($p<0.001$, OR 5.91). Clinical recurrence rate was 8% in the Kono versus 18% in the Conventional group after 12 months ($p=0.2$), and 18% versus 30.2% after 24 months ($p=0.04$, OR 3.47). Surgical recurrence rates did not differ. More confirmative studies are needed to draw definitive conclusions.

Extent of resection

Item 20
Surgical resections for CD should be as conservative as possible (EL2)
[Agreement: "Agree" 100%, round I]

Surgery for CD is not curative, and postoperative recurrence is common [143]. Fazio et al. [144] demonstrated in a randomised controlled trial that in CD surgical recurrence is unaffected by the width of resection margins (proximal margin of 2 cm vs 12 cm) from macroscopically and microscopically involved bowel.

The Lémann index assesses globally the cumulative structural bowel damage that can occur in CD [145] and surgical resection of the bowel, being irreversible, is considered the maximum level of bowel damage [146].

Item 21
The role of inclusion of the mesentery in resections for ileocolic CD has to be evaluated, and extended mesenteric resection cannot be currently recommended (EL5).
[Agreement: "Agree" 88.2%"Partially agree" 11.8%, round II]

A retrospective study by Coffey et al. [147] suggested the clinical relevance of including the mesentery in ileocolic resection for CD. The authors showed a significantly reduced reoperation rate for surgical recurrence after extended excision of the mesentery (2.9% vs 40% in the close bowel resection group). Of note, the close bowel resections referred to a historic cohort of patients in whomnot all currently available treatments were used.

While the mesentery is likely to play a pathogenic role in CD, it is also crucial for intestinal vascularization, and extensive removal may compromise bowel tissue [148] while proximal control of bleeding following extended mesenteric resection may prove difficult. Evidence suggests that morphologic and functional abnormalities in the mesenteric structures may contribute to the disease progression of CD [149], but current evidence does not support extended surgical resection of the mesentery.

Colonic disease

Acute colitis

Item 22
Patients with severe acute CD colitis as defined by the Truelove and Witts criteria, should be hospitalised (EL3) for intensive treatment with intravenous (IV) corticosteroids (EL1) and multidisciplinary surveillance is warranted (EL5)
[Agreement: "Agree" 100%, round I]

Severe acute colitis in not as common in CD as it is in ulcerative colitis (UC). Literature on the subject is quite scarce; nonetheless, the clinical picture in the two diseases appears to be similar or indistinguishable. Therefore, recommendations for treatment of acute colitis in UC can be reasonably extended to its treatment in CD [4, 32]. Severe acute CD colitis is most commonly defined, by the Truelove and Witts criteria, as the presence of bloody diarrhea > 6 times daily + 1 or more signs of systemic toxicity (tachycardia > 90 bpm, fever > 37.8 °C, hemoglobin (Hb) < 105 g/dl, erythrocyte sedimentation rate > 30 mm/hr) [3, 150–152]. This is a potentially life-threatening condition [153] requiring hospital admission. Management of the case by a multidisciplinary team is felt to be meaningful by most experts in the field, but there is lack of supporting literature [151, 154]. Once hospitalised, patients should receive general supportive treatment (intravenous fluids and electrolyte replacement, nutritional support and transfusions to maintain the Hb level over 8–10 g/dl), and appropriate investigations to exclude other aetiologies (primarily C. difficile and cytomegalovirus colitis) [151, 154]. Endoscopy in acute colitis is useful to exclude other causes of acute colitis, but should be performed by experts and with caution; in most cases a flexible sigmoidoscopy without bowel preparation is sufficient [36]. First line treatment consists of intravenous corticosteroids. This has been the established treatment for decades; it is widely available and highly effective [151].

Item 23
Efficacy of first line treatment should be evaluated by a multidisciplinary team at day 3 (EL2).
Steroid -refractory patients should receive therapy with infliximab or cyclosporine (EL1). Deterioration or failure to improve within 7 days are indications for surgery (EL2). Delaying surgical intervention beyond this time frame places patients at higher risk of mortality. (EL3).
[Agreement: "Agree" 94.1%, "Partially agree" 5.9%, round II]

Most patients respond to IV corticosteroids. Response should be assessed on the third day of therapy, unless the patient's condition deteriorates [151]. Daily laboratory tests and plain abdominal plain X-rays are recommended [3, 151]. In case of failure of first-line therapy, when the patient's condition is stable, second-line therapy with anti-TNF agents (mainly Infliximab) is the standard of care [151, 155, 156]. Second line therapy has been shown to be effective in preventing urgent surgery in 50–85% of patients. Cyclosporine has proved to be a valuable alternative in both first- and second-line management [157, 158]. Maintenance after response could be easier in responders to infliximab as compared with cyclosporine [2]. A number of predictive scores have also been developed, to identify which patients are less likely to benefit from second-line therapy and therefore candidates for early surgery [159]. Patients unresponsive to second line agents within 7 days from admission need surgery. Waiting beyond 7 days should be discouraged, as it significantly increases morbidity and mortality rates [160–163]. Randall et al. [160] reported on 80 patients with severe acute CD colitis: those who suffered a major postoperative complication had received significantly longer preoperative medical therapy (median 8 days), compared to patients without any major complications (median 5 days). In another study Bartels et al. [161] found that longer duration of preoperative medical treatment (median 15 vs 6 days) was independently associated with complication rate (42% vs 11%). A recent study by Leeds et al. [163] including 508 patients, goes further and reports an impressive four times higher mortality (20% vs 5%) in their "delayed surgery" group, compared to the "early surgery" one. The delayed surgery group had surgery a median of 6 days after admission, the early group after only 1 day. This is much earlier than in other studies, where both groups may have been considered as "early surgery". Hence, while this study may further shift the trend towards operating earlier, it should be stressed that immediate operation is, in most instances, over-treatment as the great majority of patients respond to drugs and this attitude may lead to missed opportunities for bowel salvage. A third line of therapy has been reported to have acceptable results but the evidence in its favor is probably still outbalanced by the risks of not operating [164, 165].

Item 24
When surgery is needed, the operation of choice is subtotal colectomy (EL2). Optimal management of the rectal stump after urgent subtotal colectomy is unclear. There is no evidence to support any technique over the others (EL4)
[Agreement: "Agree" 100%, round II]

When surgery is indicated for complications or failure of treatment the procedure of choice is subtotal colectomy and

terminal ileostomy, with division of the colon at the level of the distal sigmoid colon [3, 32, 154, 166]. This procedure avoids the morbidity associated with pelvic dissection, while allowing the patient to recover good general health. Nonetheless it carries a burden of 2–8% mortality and a 40% morbidity [165]. Total proctocolectomy is associated with high morbidity in this setting [167] and is generally not indicated for acute CD colitis.

Item 25
When sufficient expertise is available colectomy can be performed laparoscopically in the urgent setting, with a shorter hospital stay and less postoperative complications (EL2). If conditions permit, patients should be referred to highly experienced centers (EL3)
[Agreement: "Agree" 88.2%, "Partially agree" 5.9%, "Disagree" 5.9, round II]

The laparoscopic approach is the standard of care in elective IBD surgery [32, 168]. In recent years laparoscopy has been investigated in urgent colectomy as well. No randomised study exists. Many large retrospective studies comparing open and laparoscopic techniques have reported their results [169–173]. The conversion rate was low, major complication and mortality rates were similar, length of stay was shorter, and the infection rate was lower in the laparoscopic group. In one study, subsequent restorative surgery was performed significantly earlier in the laparoscopic group [173]. These results have been confirmed in a systematic review and meta-analysis comprising 966 patients [162]; the pooled conversion rate was 5.5% (95% CI 0.3.6–8.4), the pooled risk of wound infection was 0.60 (95% CI 0.38–0.95; $p=0.03$) and that of intra-abdominal abscess was 0.27 (95% CI 0.08–0.91; $p=0.04$), both in favor of laparoscopic surgery, with similar additional complications rates. Length of stay was shorter after laparoscopic surgery, with a pooled mean difference of 3.17 (95% CI 2.37–3.98) days ($p<0.001$). These studies provide convincing evidence of the benefit of laparoscopy even in the urgent setting and therefore this should be the approach of choice where expert surgeons are available. It should be highlighted however that these results come from high volume hospitals with great expertise in IBD and laparoscopy. The considerations above are not applicable to unstable/critically ill patients (with toxic megacolon for instance) in need of emergency colectomy. Strong evidence suggests that surgeon experience with colectomies in IBD is a major factor affecting mortality in non-elective surgery. In a Danish study comparing elective and urgent colectomy for IBD, very low (< 3) or low (3–12) total colectomy volume was significantly associated with higher mortality rates (11.3% vs 5.9 vs 3.6%) [174]. In another study, by Justiniano et al. [175], analysing the effect of various factors on 15,000 resections for IBD in the non-elective setting, hospital level variation accounted for a 23-fold difference in mortality. It is therefore advisable that patients who are not critically ill, should be quickly transferred to experienced centers for optimal surgical management. When the patient's condition is too unstable for transfer, a safe option could be temporary ileostomy with transfer after improvement. Although it should not be regarded as the procedure of choice, the ileostomy strategy, has been reported in a small study to be associated with minimal morbidity and could offer the patient an opportunity to receive subsequent major surgery in an expert center [176].

Colonic strictures

Item 26
The treatment of choice for large bowel stricture is balloon dilatation (provided the segment can be extensively assessed and surveyed) or segmental resection. We advise against SP (EL3)
[Agreement: "Agree" 82.35%, "Partially agree" 17.65%, round II]

Adapted from 2018 ECCO-ESCP consensus on surgery for CD [32]. Luminal narrowing of the colon is not uncommon in colonic CD. Although obstructive symptoms from colonic strictures occur in up to 17% of patients even in absence of obstructive symptoms, colonic stricture harbors occult carcinoma in 7% of cases [4]; it must be assessed with multiple endoscopic biopsy and may hamper further colonoscopic surveillance of proximal colon.

The upfront treatment for short strictures of the colon and ileocolonic anastomosis is balloon dilatation as reported in recent systematic reviews and in the largest cohort of its kind [32, 33, 177].

In case of technical failure surgical segmental resection is suggested. Although there is a greater risk of recurrence than after more extensive resection, it guarantees a lower risk of permanent stoma as reported in a systematic review [178]. There are no data concerning biologic treatment after segmental colectomies.

SP has been proposed for short segmental colonic strictures but it cannot be recommended due to lack of evidence of benefit over segmental resection and potential risk of misdiagnosed cancer [4, 32].

Endoscopic stent placement or endoluminal injection of anti-TNFalpha or steroids are an option but there is no data to recommend the routine use of these techniques [33, 177].

Endoscopic stricturotomy is an alternative technique to treat anastomotic strictures but there are still not sufficient evidence to support the advantages of the procedure over dilatation or surgery and further studies are needed [179].

Approximately 7% of colonic strictures harbor occult carcinoma. Stenosis is more commonly associated with cancer in advanced age, longer duration of disease or history of low-grade dysplasia [180, 181]. Any colorectal stricture should be extensively assessed with multiple endoscopic biopsies to ensure the absence of malignancy. This is possible only if dilation resolves the stenosis. If the stricture cannot be adequately surveyed resection of the affected large intestine should be performed.

Fate of the rectum

Item 27
A subtotal colectomy with end ileostomy is preferable in case of colitis in CD patients with severe rectal involvement. If the rectum is not involved, an ileorectal anastomosis is a safe option (EL2)
[Agreement: "Agree" 87.50%, "Partially agree" 6.25%, "Disagree" 6.25%, round I]
Item 28
Endoscopic surveillance is mandatory due to the risk of developing cancer in the rectal stump (EL2)
[Agreement: "Agree" 93.75%, "Partially agree" 6.25%, round I]

Crohn's colitis unresponsive to medical treatment often requires a subtotal colectomy. Colectomy has been shown to be associated with a lower rate of recurrence than segmental resections [178, 182].

In up to 36% of patients undergoing colectomy for CD, an end ileostomy is constructed and the rectal stump is left in situ [183, 184]. The tendency is to avoid anastomosis in case of severe perianal disease or active Crohn's proctitis, even though an ileorectal anastomosis offers the patient a better quality of life and avoids the risks related to the presence of a stoma [185, 186].

An underestimated complication of a diverted rectal stump is diversion proctitis, a condition associated with abdominal pain, tenesmus, and purulent rectal discharge [187], which is reported by up to 90% of patients [188].

Data regarding the risk of neoplastic degeneration of the rectal stump are lacking. In a recent meta-analysis, the rate of cancer was shown to be 2.1% and 2.4% in patients with a diverted rectal stump or ileorectal anastomosis, respectively [189]. Associated risk factors were duration of disease, history of colorectal cancer, and primary sclerosing cholangitis.

When needed, proctectomy can be performed via a minimally invasive transanal approach [190], provided that the operating surgeon has adequate expertise and qualifications. The results of this approach need to be further elucidated.

Ileoanal pouch

Item 29
IPAA can be successful in carefully selected CD patients. Only highly motivated CD patients with isolated colitis without active perianal disease can be considered for restorative proctocolectomy (EL3)
[Agreement: "Agree" 88.2%, "Partially agree" 11.8%, round II]

Suboptimal results have been reported in the past after ileal pouch-anal anastomosis (IPAA) in CD patients [191, 192]. Selection of a specific phenotype of CD for surgery increases the likelihood of IPAA success [193]. A careful preoperative evaluation should include perineal examination combined with imaging to rule out fistulas and small bowel disease. It is recommended to create a J pouch with a stapled pouch-anal anastomosis and no mucosectomy to minimize sphincter damage [32].

In comparison with older data from multiple case series [194, 195] that showed quite high pouch failure rates and pouch complications, more recent studies have reported better results with good pouch retention rates in selected CD patients [196–198].

Most importantly, a consistent amount of data seems to underline that CD-IPAA patients who retain their pouches are satisfied [196], scoring on par with UC-IPAA patients on quality of life surveys regarding dietary, social, work or sexual restrictions [193].

It appears reasonable to propose pouch surgery in selected patients with colorectal CD in whom the only alternative is definitive end-ileostomy [196, 199].

Potential candidates for pouch surgery should be counseled extensively about the possibility that the development of CD of the pouch may lead to pouch loss or necessitate further treatment [196], and that surveillance is necessary [200, 201].

Item 30
A known diagnosis of CD at the time of pouch surgery (intentional IPAA) is related to a lower risk of CD manifestations of the pouch and pouch failure in comparison with a delayed or unsuspected diagnosis of CD (EL3)
[Agreement: "Agree" 56.25%, "Partially agree" 25%, "Neutral" 12.50%, "Disagree"6.25%, round I]

Most of the literature investigating pouch outcomes in patients with CD is retrospective and, given the tendency to avoid IPAA in known CD, is primarily composed of patients with a preoperative diagnosis of UC who underwent IPAA and present in a delayed fashion with symptoms and/or complications typical of CD.

The long-term evolution of CD in patients with CD diagnosed before or immediately following pouch surgery appears to be less aggressive than in patients diagnosed later. Patients with Crohn's colitis with late complications likely represent a group of patients predisposed to transition phenotypically to CD with small bowel involvement and more severe ongoing disease [202].

Incidental IPAA for CD is associated with a high rate of failure but also an acceptable long-term functional results if the pouch can be kept functioning in situ [196, 203]. Intentional IPAA for CD is associated with lower rates of failure [196].

The decision to perform restorative proctocolectomy in CD patients should be made after an extensive discussion among multidisciplinary team members of a tertiary center with experience in the management of these complex cases, and after an honest and clear discussion with the patient and their family.

Crohn's disease management after surgery

Postoperative treatment of Crohn's disease

Item 31
The strongest predictors of postoperative recurrence after ileocolonic resection are active smoking, history of resectional surgery for CD (EL1), penetrating disease pattern, length of small bowel resection, perianal disease (EL2), myenteric plexitis (EL3), and absence of prophylactic treatment (EL1)
[Agreement: "Agree" 100%, round I]

Item 32
Patients with CD should be encouraged to stop smoking after surgery (EL1)
[Agreement: "Agree" 94.1%, "Partially Agree" 5.88%, round I]

Recurrence after intestinal resection remains a significant problem in the postoperative management of CD. The surgical recurrence generally follows the clinical recurrence. According to a systematic review with metanalysis [204] the 10-year-after-primary-surgery cumulative rate of surgical recurrence in studies conducted after 1980 was of 33% (95% CI 31–35%), that is lower than earlier studies reporting a rate of 45% (95% CI 38–53%). The most significant factor that predicted postoperative recurrence was patient smoking status (OR 2.1; 95% CI 1.42–3.27) [205]. Other risk factors for relapse were previous resection, fistulizing phenotype (B3), extensive small bowel resection (> 50 cm), perianal disease, severe myenteric plexitis, and the absence of postoperative prophylactic treatment [143, 206, 207].

Item 33
Postoperative prophylactic treatment of CD depends on the presence of risk factors for relapse and should be considered in patients who have at least one of the recognized risk factors (EL2)
[Agreement: "Agree" 100%, round I]

Anti-TNF-α and thiopurine drugs have been shown to be effective to decrease the early relapse when compared with traditional therapy (antibiotics, aminosalicylates, budesonide alone or probiotics) [208]. Peyrin-Biroulet et al. recommended the use of thiopurines in patients with only one risk factor, while in those with two or more risk factors anti-TNF-α drugs are preferred [206]. Results from the POCER randomized clinical trial demonstrated that two or more clinical risk factors, including smoking (OR 2·8, 95% CI 1·01–7·7, $p = 0{\cdot}05$), increased the risk of endoscopic recurrence of CD and that anti-TNF-α drugs are the most effective therapy for prevention of recurrence [209]. In CD patients at high risk of postoperative relapse adalimumab is more effective than thiopurines in preventing early recurrence [210]. In a recent systematic review with network meta-analysis, anti-TNF-α therapies alone, or in combination, are considered the best drugs to prevent endoscopic relapse of CD [211]. A large randomized clinical trial, the PREVENT study, evaluated the role of anti-TNF-α agents in preventing relapse of CD after surgical resection: patients were assigned to receive either postoperative infliximab or placebo. This study showed that endoscopic recurrence at week 76, was significantly different between the infliximab group and the placebo group (22.4% vs. 51.3%, $p < 0.001$) although there was no statistically significant difference in clinical recurrence (12.9 vs. 20.0%, $p = 0.097$) [208]. Tursi et al. demonstrated that infliximab and adalimumab were similar to avoid the histological, endoscopic, and clinical recurrence after curative ileocolonic resection in high risk CD patients [212].

Item 34
Ileocolonoscopy performed within the first year after surgery, ideally between 6 and 12 months postoperatively, is the most effective diagnostic tool for detecting relapse (EL2).
[Agreement: "Agree" 94.1%, "Partially Agree" 5.88%, round I]

The postoperative clinical course of CD is best predicted by the degrees of the endoscopic lesions [26]. Ileocolonoscopy at 6–12 months after surgery is recommended for the early detection of postoperative recurrence [36]. Endoscopic recurrence in the neo-terminal ileum

should be classified using the modified Rutgeerts score [10, 213]. Endoscopic monitoring followed by a step-up treatment approach has been shown to be more effective than conventional drug therapy alone in reducing clinical and endoscopic recurrence [209].

Recurrences can occur also after other-than-ileocolic resection (e.g. small bowel), and might be more difficult to assess. Besides, it would be desirable to have less invasive methods to follow up patients, e.g. ultrasonography. However, no definitive data are available.

Perianal disease

Perianal abscess and fistula

Item 35
Even though there is no consensus, perianal fistulas are usually classified as "simple" or "complex" (EL5)
[Agreement: "Agree" 100%, round II]
Item 36
Contrast-enhanced pelvic MRI should be the first procedure both for initial diagnosis and assessment of perianal abscesses and fistulae and for appraisal of the results of treatments (EL2). A good alternative is represented by endoscopic or endo-anal ultrasound (EAUS), if anorectal stenosis is excluded (EL2). Both diagnostic exams are more accurate if combined with examination under anesthesia (EUA) (EL1).
[Agreement: "Agree" 94.1%, "Disagree" 5.9%, II round]
Item 37
If an abscess is present, EUA with hydrogen peroxide enhancement with consensual abscess drainage is considered the gold standard procedure when performed by an experienced surgeon, since it allows diagnosis and treatment at the same time, unless a pelvic MRI scan is immediately available. (EL5).
[Agreement: "Agree" 94.1%, "Disagree" 5.9%, round II]

Perianal fistulas in CD can be classified following the Parks' classification [214], but in 2003 the American Gastroenterological Association (AGA) proposed a more clinically useful classification, distinguishing fistulas into simplex or complex [215]. Perianal fistulas develop in 14–23%, of patients with CD 23%, reaching 42% after a 20-year history of the disease [216–219]. A recent analysis of 1970 patients with perianal abscess, found that progression to subsequent fistula occurred in 16% of patients after a median of 7 months; however, CD patients were more than twice as likely to develop a fistula (OR = 2.5, 1.7–3.7) [220]. Fistulas may precede or appear simultaneously with intestinal symptoms [216, 218, 221]. In a series of 202 patients with CD, 54% presented with perianal complications [222]. The risk of fistulising complications also depends on disease location reaching 90% in colonic disease involving the rectum [223]. The diagnostic approach is important because the findings influence the therapeutic strategy. Various tools have been described, including EUA and imaging by EAUS or pelvic MRI [224, 225]. EAUS is reported to have an accuracy of 90% [216, 221]. MRI has an accuracy of 76–100% compared to EUA and may provide additional information. When any of the imaging modalities are combined with EUA the accuracy is 100% [216]. When performed by experts, EUA can have an accuracy up to 100% [226], with the advantage of allowing concomitant surgery. These methods should be combined with endoscopy since colorectal inflammation should be treated as well [227, 228]. There is no general consensus about classification of perianal fistulae. From the surgical point of view Parks' classification, based on the relationship of any tract to the sphincter complex, is more descriptive and can guide surgical decisions, but it is complicated to use in routine practice. Empiric classifications into simple and complex fistulae has been proposed [229, 230], where a simple fistula is low, has a single external opening, has no abscess, has no evidence of a rectovaginal fistula, and has no evidence of anorectal stricture. Occurrence of treatment-related abscesses, due to a "false" closure of the fistula, is a concern after anti-TNF alpha treatment, when the definition of "healing" is based only on clinical examination [231–233]. Rasul demonstrated that while infliximab produced clinical remission in 49% of patients, complete radiological healing occurred in only 6% of the patients [234]. Complete healing of perianal fistulas should be ruled out by combining robust clinical and radiological evaluation with MRI to have 100% accuracy [216, 235, 236].

Following the increasing attention paid to three-dimensional (3D) imaging and 3D printing in colorectal surgery [237–239], Some authors have proposed the utility of 3D imaging and printed models to improve the understanding of complex fistulae, to ease discussion with patients, and facilitate surgical simulation [240, 241]. 3D images can be viewed on smartphones [242], making such imaging modality an attractive tool in the operation theater. Further studies should address the actual role of these emerging technologies.

Item 38
When symptomatic, a simple perianal fistula requires combined medical and surgical treatment. Antibiotics (metronidazole and/or ciprofloxacin) and surgical drainage of sepsis and loose seton placement is the preferred strategy (EL3). Uncomplicated superficial anal fistula (submucosal / subcutaneous) can be treated by simple fistulotomy (EL5)
[Agreement: "Agree" 100%, round II]

Item 39
In complex fistulas, EUA with surgical drainage of the abscesses, fistulectomy and loose seton placement should be performed, possibly after diagnostic imaging assessment (EL2). Infliximab (EL1) or adalimumab (EL2) should be used as first-line therapy following adequate surgical drainage
[Agreement: "Agree" 88.2%, "Partially agree" 5.9%, "Disagree" 5.9%, round II]

Simple fistulas represent an indication for surgical treatment when symptomatic. EUA is indicated, preceded by pelvic MRI or EAUS, for drainage of sepsis and loose seton placement [186, 243, 244]. When combined with optimal medical therapy, seton can be removed in up to 98% of cases [245]. Cutting setons are not recommended due to the high risk of incontinence (57%), caused by the transection of the anal sphincter [246, 247]. Fistulotomy can be considered in selected patients with subcutaneous/submucosal fistulas [243, 248] with healing rates up to 100% [249]. First-line treatment is biological therapy preceded by surgical drainage and seton placement possibly performed after diagnostic imaging [218, 250, 251]. Closure rates of 13.6–100% after biologic treatment are reported [243–245, 251–254]. The best results are achieved if anti-TNF alpha therapy and surgical drainage of sepsis are combined, with a higher healing rate, longer duration or healing and a low recurrence rate [251, 255–258]. Limited experiences suggest that local injection of infliximab/adalimumab performed at the internal orifice, could be beneficial in patients with contraindications to systemic anti-TNF-alpha [259–262]. Mucosal endoanal advancement flap can be proposed for highly selected patients with perianal/vaginal fistulas and rectal sparing or mucosal healing after biological therapy [263]. This procedure can lead to a primary closure of the fistula and can be safely repeated to increase the healing rate [264–266]. Efficacy of anal fistula plugs, fixed into the fistula's primary opening and acting as a scaffold for new tissue growth has been reported, but results are disappointing when used in patients with CD [267–270]. Likewise, the role of collagen paste seems safe and moderately effective [271]. Video-assisted fistula treatment (VAAFT) has been reported to ameliorate the symptoms of CD patients with perianal disease and it could be an interesting "palliative" tool [270, 272]. Ostomy or proctectomy may be necessary for refractory severe disease. Fecal diversion is effective in improving quality of life, but only one-fifth of patients are stoma-free in the long term. Diversion is preferable to proctectomy because of perianal complications or impaired healing of perianal wounds. Diversion rates range from 31 to 49% [229, 273]. Concomitant colonic disease, previous temporary diversion, fecal incontinence, and anal canal stenosis are reported as predictive factors. Despite optimal medical and minimally invasive therapy, 8–40% of patients will require proctectomy to control symptoms [256, 274, 275].Proctectomy can be performed with minimally invasive transanal surgery [190]. Perineal sepsis is associated with wound complications after proctectomy [276]. In patients with failed ileorectal anastomosis, candidates for proctectomy because of active rectal and perianal disease, infliximab can be of help in delaying or avoiding proctectomy [277].

Cell-based therapy

Item 40
In difficult-to-treat multi-resistant patients, who failed combined therapy and/or surgical repair, local injection of autologous/allogenic mesenchymal stem cells [EL 2] or micro-fragmented adipose tissue [EL 4] may be considered. Indications, dosage, combination with other agents and number of treatments still need to be explored (EL 4)
[Agreement: "Agree" 87.50; "Neutral" 12.50%, round I]

Patients unresponsive to combined bio-surgical therapy may benefit from innovative approaches such as regenerative medicine by means of local injection of mesenchymal stromal cells (MSCs). MSCs influence the microenvironment through trophic, immunomodulatory and anti-microbial actions [278–280]. Bone marrow and adipose tissue are the most readily available sources of MSCs, and adipose tissue is preferable because of its abundance, easy access, and the simple isolation procedure [281]. MSCs derived from bone marrow [282] or adipose tissue [236, 283–285] have been used, without side effects, in the treatment of refractory perianal CD in phase II and III clinical trials [286, 287]. Garcia-Olmo combined fibrin glue with adipose tissue stem cells (ASCs) achieving short-term success in more than 70% of patients, which decreased in the long-term to 58% [288]. A subsequent phase III multicenter controlled trial, confirmed these favorable results only in the author's center [289]. Using local injection of bone marrow MSCs, not only local success but also attenuation of systemic inflammation was reported [290] and in a series of 10 patients treated with ASC infiltration, a complete fistula closure rate of 44.4% was reported [291]. The ADMIRE-CD-Group in a phase-III-randomised trial showed a 50% rate of combined remission (clinical assessment confirmed by MRI) at 24 weeks after a single local administration of allogenic ASCs (Cx601) combined with closure of the internal opening by suture; results seem good at 52-week follow-up [236, 285]. However, the study aimed at remission rather than cure of the fistula and patients with an abscess smaller than 2 cm at MRI without

clinical impact were considered as pertaining to the endpoint met group. In a dose-finding study by Molendijk [292], patients were randomized to treatment with a single injection of 1 of 3 doses: the 2 doses with the highest efficacy were 1×107 and 3×107 cells. Daily practice is limited by the need of good manufacturing practice (GMP) laboratories, time, and costs of in-vitro cell expansion, and restrictions related to cell manipulation [293]. Novel approaches which should possibly be "one-step", minimally invasive, not requiring any enzymatic treatment [294], less expensive and compliant with health regulations are required. In a prospective study with 15 multi-resistant complex perianal CD patients, a 66.7% rate of combined healing was obtained with a single administration of autologous microfragmented adipose tissue obtained by liposuction and prepared by minimal manipulation with a non-enzymatic method [295]. Combined remission in 60% of patients using adipose-derived stromal vascular fraction (ADSVF) with an enzymatic method was reported [296].

Perianal conditions other than fistula

Item 41
Skin tags
Medical treatment is the best option, consisting of sitz baths, medications to regulate bowel movements and topical treatments to protect the skin, relieve symptoms and improve healing (EL3)
Surgery is not supported by the literature and should be avoided because of the risk of poor healing and septic complications (EL3).
[Agreement: "Agree" 100%, I round]

Patients with CD can have several anoperineal lesions [297–299]. Anal skin tags are typical manifestation of CD. They are usually classified into two different groups, type 1 (also called "elephant ears") and type 2. Type 1 are typically soft and painless external lesions, whereas the type 2 skin tags are hard, edematous, irregular, cyanotic and more commonly painful, often associated with hemorrhoids [300]. Skin tags are present in approximately 11% of patients with CD [301] and are generally asymptomatic but may become edematous and enlarged during a CD flare. When that happens they may cause worsening pruritus and interfere with perianal hygiene [302]. If needed, medical treatment is often effective while there is no evidence in the literature about the benefits of surgical treatment, this because of the risk of poor wound healing. For this reason, when there is active inflammation, surgical management should be avoided [222].

Item 42
Hemorrhoids
The first line treatment for symptomatic hemorrhoids in patients with CD is systemic and topical medical therapy. This is effective in more than 60% of cases and should be promptly considered in case of CD flare (EL2)
[Agreement: "Agree" 100%, round I]
Item 43
Hemorrhoids
Results of surgical treatment are controversial with a high risk of septic complications. Non-invasive techniques could be considered for patients with hemorrhoids and CD but further studies are needed (EL3)
[Agreement: "Agree" 94.12%, "Disagree"5.9%, round II]

Hemorrhoids are uncommon in CD, with a reported incidence of 7% [222]. Conservative therapy is always the first line treatment. Rubber band ligation may be helpful but there is no evidence regarding this in the literature [230]. Surgical treatment of hemorrhoids in CD is associated with a high complication rate and is only reluctantly advocated [303]. However, Wolkomir [304] described a series of 17 patients with quiescent intestinal CD who underwent hemorrhoidectomy. At 2 months the healing rate was 88%, and only one patient developed disease progression requiring a proctectomy 15 years later [304]. Similarly, McKenna et al. [305] suggested that carefully selected IBD patients could benefit from surgical treatment of hemorrhoidectomy, as the authors stated that the requirement for subsequent proctectomy appeared to be secondary to the natural disease course of perianal CD rather than perianal intervention In another study conservative treatment was effective in more than 60% of the 45 CD patients with hemorrhoids in. Those with persistent symptoms underwent surgery or rubber band ligation; 41% of patients had postoperative complications, including bleeding, anal fissure, and perianal sepsis. No patients required proctectomy [306].

Doppler-guided hemorrhoidal artery ligation (DGHAL) is an alternative to hemorrhoidectomy. Karin reported that 77% of asymptomatic patients treated with DGHAL for grade III hemorrhoids at 18 months had no postoperative complications, but only 13 patients were included [307]. DGHAL may be a safe, less invasive alternative to conventional hemorrhoidectomy in patients with refractory CD-associated hemorrhoids [303], but further studies are warranted.

Item 44
Fissure
The first line treatment of anal fissures is conservative, with systemic and topical medications for controlling bowel movements and improve tissue healing. (EL3)
If these fail, surgery (lateral internal sphincterotomy) could be considered, provided that there is no active rectal disease (EL4)

The role of topical botulinum toxin, and other pharmacologic agents that relax the anal sphincter for the treatment of anal fissures in patients with CD is unknown, but they seem a safe option (EL5) [Agreement: "Agree"94.1%, "Neutral" 5.9%, round II]

Anal fissures are the most frequent manifestation of perianal CD with a reported incidence of 21–35% [301, 308, 309]. They result from a direct ulceration of the tissues, not related to the resting anal sphincter pressure [310], presenting as large and deep ulceration, often located in the posterior midline but also in multiple locations. Anal fissures may be symptomatic with different degrees of pain, bleeding, discharge and pruritus. In case of pain the presence of an abscess or fistula must be excluded [311, 312]. The first line treatment is conservative with systemic and topical medications for controlling bowel movements and improve tissue healing. Although the use of topical sphincter relaxants, such as calcium channel blockers and nitro-glycerine, and botulinum toxin has been reported in non-CD patients [313, 314], its role in CD patients is unknown. When medical therapy is not effective, surgery should be considered, but only a few retrospective studies have reported the outcome of surgical treatment for anal fissure in CD. In a study by Wolkomir [304], 25 patients with CD had surgery for anal fissures, the majority consisting of internal sphincterotomy and 88% healed at 2 months. Over a mean follow-up period of over 7 years, only two required proctectomy because of progression of primary disease and not because of the fissure operation performed. In a series with 56 patients, Fleshner et al. [312] found that fissures were more likely to heal after internal sphincterotomy than after medical treatment alone. Anorectal surgery can be safe only in carefully selected patients with CD and rectal sparing who have failed medical management, although larger, randomized studies are needed.

Conclusions

There was good agreement overall, but the committee felt that there are several areas of CD management that need further attention.

These include the role of strictureplasty, the extent of resection in CD, and perianal disease.

Future studies should assess these aspects of CD.

The resulting recommendations need to be applied carefully, after taking into account the individual features of each patient, and after a clear discussion with the patient about all the available options for each specific condition, and realistic expectations.

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Compliance with ethical standards

Conflict of interest The authors declares that they have no conflict of interest.

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