Manuscript Doi: 10.1093/ecco-jcc/jjae089

ECCO Guidelines on Therapeutics in Crohn's Disease:

Surgical Treatment

Michel Adamina[1,2], Silvia Minozzi, Janindra Warusavitarne, Christianne Buskens, Maria Chaparro, Bram Verstockt, Uri Kopylov, Manasi Agrawal, Mariangela Allocca, Raja Atreya, Robert Battat, Dominik Bettenworth, Gabriele Bislenghi, Steven Ross Brown, Johan Burisch, María José Casanova, Wladyslawa Czuber-Dochan, Joline de Groof, Alaa El-Hussuna, Pierre Ellul, Catarina Fidalgo, Gionata Fiorino, Javier Gisbert, João Guedelha Sabino, Jurij Hanzel, Stefan Holubar, Marietta Iacucci, Nusrat Iqbal, Christina Kapizioni, Konstantinos Karmiris, Taku Kobayashi, Paulo Gustavo Kotze, Gaetano Luglio, Christian Maaser, Gordon Moran, Nurulamin Noor, Konstantinos Papamichail, Georgios Peros, Catherine Reenaers, Giuseppe Sica, Rotem Sigall-Boneh, Stephan R. Vavricka, Henit Yanai, Tim Raine, Hannah Gordon, Pär Myrelid

Michel Adamina	1. Department of Surgery, Cantonal Hospital of Fribourg & Faculty of Science and Medicine, University of Fribourg, Fribourg, Switzerland 2. Department of Visceral and Thoracic Surgery, Kantonsspital Winterthur, Winterthur, Switzerland
Silvia Minozzi	Department of Epidemiology, Lazio Regional Health Service, Rome, Italy
Janindra Warusavitarne	St Mark's Hospital London; United Kingdom
Christianne Johanna Buskens	Department of Surgery, Amsterdam UMC, Location VUMC, Amsterdam, The Netherlands
Maria Chaparro	Gastroenterology Department. Hospital Universitario de La Princesa, Instituto de Investigación Sanitaria Princesa (IIS-Princesa), Universidad Autónoma de Madrid (UAM), Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBEREHD), Madrid; Spain
Bram Verstockt	Department Gastroenterology & Hepatology, University Hospitals Leuven, KU Leuven and Dpt. Chronic Diseases and Metabolism, KU Leuven, Leuven, Belgium
Uri Kopylov	Department of Gastroenterology, Sheba Medical Center, Ramat Gan, Israel
Henit Yanai	IBD Center, Division of Gastroenterology, Rabin Medical Center, Petah Tikva; Faculty of Medicine, Tel Aviv University, Tel Aviv; Israel
Stephan R. Vavricka	Department of Gastroenterology and Hepatology, University Hospital Zürich, Zürich, Switzerland
Rotem Sigall-Boneh	Pediatric Gastroenterology and Nutrition Unit, The E. Wolfson Medical Center, Holon, Israel. Tytgat Institute for Liver and Intestinal Research, Amsterdam Gastroenterology Endocrinology and Metabolism, University of Amsterdam, Amsterdam, the Netherlands
Giuseppe S. Sica	Department of Surgery, Università Tor Vergata, Roma, Italy

© The Author(s) 2024. Published by Oxford University Press on behalf of European Crohn's and Colitis Organisation. All rights reserved. For permissions, please email: journals.permissions@oup.com

Accepted Manuscript

Downloaded from https://academic.oup.com/ecco-jcc/advance-article/doi/10.1093/ecco-jcc/jjae089/7693896 by KU Leuven Libraries user on 04 July 2024

Manuscript Doi: 10.1093/ecco-jcc/jjae089

Catherine Reenaers	Gastroenterology Department, Chu Liege, Liege, Belgium
Georgios Peros	Department of Surgery, Cantonal Hospital Winterthur, Winterthur, Switzerland
Konstantinos Papamichael	Center for Inflammatory Bowel Diseases, Division of Gastroenterology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts
Nurulamin Noor	Department of Medicine, University of Cambridge, Cambridge, United Kingdom
Gordon William Moran	1. National Institute of Health Research Nottingham Biomedical Research Centre, University of Nottingham and Nottingham University Hospitals, Nottingham 2. Translational Medical Sciences, School of Medicine, Faculty of Medicine and Health Sciences, University of Nottingham, Nottingham. NG7 2UH. United Kingdom
Christian Maaser	Outpatients Department of Gastroenterology, University Teaching Hospital Lueneburg, Germany
Gaetano Luglio	Department of Public Health, University of Naples Federico II, Naples, Italy
Paulo Gustavo Kotze	Health Sciences Postgraduate Program, Pontificia Universidade Católica do Paraná (PUCPR), Curitiba, Brazil
Taku Kobayashi	Center for Advanced IBD Research and Treatment, Kitasato University Kitasato Institute Hospital, Tokyo, Japan
Konstantinos Karmiris	Department of Gastroenterology, Venizeleio General Hospital, Heraklion, Greece
Christina Kapizioni	Department of Gastroenterology, Attikon University Hospital, Athens, Greece
Nusrat Iqbal	Department of Surgery, Worcestershire Acute Hospitals NHS Trust, Worcester, UK.
Marietta Iacucci	APC Microbiome Ireland, College of Medicine and Health, University College of Cork, Cork, Ireland
Stefan Holubar	Department of Colon & Rectal Surgery, Cleveland Clinic, Cleveland, Ohio, USA
Jurij Hanzel	Department of Gastroenterology, University Medical Centre Ljubljana, Ljubljana; Chair of Internal Medicine, Faculty of Medicine, University of Ljubljana, Ljubljana, Slovenia
João Guedelha Sabino	Department of Gastroenterology and Hepatology, University Hospitals Leuven, Leuven, Belgium
Javier P. Gisbert	Gastroenterology Department. Hospital Universitario de La Princesa, Instituto de Investigación Sanitaria Princesa (IIS-Princesa), Universidad Autónoma de Madrid (UAM), Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBEREHD), Madrid, Spain
Gionata Fiorino	IBD Unit, San Camillo-Forlanini Hospital, Rome, Italy
Catarina Fidalgo	Division of Gastroenterology, Hospital Beatriz Ângelo, Loures Division of Gastroenterology, Hospital da Luz, Lisboa Portugal
Pierre Ellul	Division of Gastroenterology, Mater Dei Hospital, Malta
Alaa El-Hussuna	OpenSourceResearch Organization (OSRC.Network), Aalborg, Denmark
Joline de Groof	Colorectal Surgery, Royal Surrey NHS Foundation Trust, Guildford, UK
Wladyslawa Czuber-Dochan	Florence Nightingale Faculty of Nursing- Midwifery and Palliative Care, King's College London, London, United Kingdom
María José Casanova	Gastroenterology Department. Hospital Universitario de La Princesa, Instituto de Investigación Sanitaria Princesa (IIS-Princesa), Universidad Autónoma de Madrid (UAM), Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y

Accepted Manuscript

Downloaded from https://academic.oup.com/ecco-jcc/advance-article/doi/10.1093/ecco-jcc/jjae089/7693896 by KU Leuven Libraries user on 04 July 2024

Manuscript Doi: 10.1093/ecco-jcc/jjae089

	Digestivas (CIBEREHD), Madrid. Spain
Johan Burisch	Gastrounit, Medical Division, Copenhagen University Hospital - Amager and Hvidovre, Hvidovre; Copenhagen Center for Inflammatory Bowel Disease in Children, Adolescents and Adults, Copenhagen University Hospital - Amager and Hvidovre, Hvidovre, Denmark
Steven Ross Brown	Department of Surgery, Sheffield Teaching Hospitals, Sheffield UK
Gabriele Bislenghi	Department of Abdominal Surgery, University Hospitals Leuven, Belgium
Dominik Bettenworth	CED Schwerpunktpraxis, Münster and Medical Faculty of the University of Münster, Münster, NRW, Germany
Robert Battat	Division of Gastroenterology, Centre Hospitalier de l'Université de Montréal, Montreal, Canada
Raja Atreya	First Department of Medicine, Friedrich-Alexander-University Erlangen-Nürnberg, Erlangen, Germany.
Mariangela Allocca	IRCCS Hospital San Raffaele and University Vita-Salute San Raffaele, Gastroenterology and Endoscopy, Milan, Italy
Manasi Agrawal	1. The Dr. Henry D. Janowitz Division of Gastroenterology, Icahn School of Medicine at Mount Sinai, New York, New York, USA 2. Center for Molecular Prediction of Inflammatory Bowel Disease (PREDICT), Department of Clinical Medicine, Aalborg University, Copenhagen, Denmark
Tim Raine	Department of Gastroenterology, Addenbrooke's Hospital, Cambridge University Hospitals NHS Foundation Trust, Cambridge, United Kingdom
Hannah Gordon	Translational Gastroenterology and Liver Unit, University of Oxford, Oxford, UK
Pär Myrelid	Department of Surgery and Department of Biomedical and Clinical Sciences, Linköping University, Linköping, Sweden

Corresponding author: Prof. Dr. Michel Adamina, MD, PD, MSc, EMBA HSG, FEBS, FASCRS, Chairman, Department of Surgery, Cantonal Hospital Fribourg, Chemin des Pensionnats 2/6, 1752 Villars-sur-Glâne, Switzerland. Tel. +41 26 306 25 10; Email michel.adamina@gmail.com

Accepted Manuscript

Downloaded from https://academic.oup.com/ecco-jcc/advance-article/doi/10.1093/ecco-jcc/jjae089/7693896 by KU Leuven Libraries user on 04 July 2024

Manuscript Doi: 10.1093/ecco-jcc/jjae089

Abstract

This article is the second in a series of two publications on the European Crohn's and Colitis Organisation [ECCO] evidence-based consensus on the management of Crohn's disease. The first article covers medical management; the present article addresses surgical management, including preoperative aspects and drug management before surgery. It also provides technical advice for a variety of common clinical situations. Both articles together represent the evidence-based recommendations of the ECCO for Crohn's disease and an update of prior ECCO guidelines.

Keywords: Crohn's disease; Surgery; Inflammatory bowel disease (IBD)

Accepted Manuscript

Downloaded from https://academic.oup.com/ecco-jcc/advance-article/doi/10.1093/ecco-jcc/jjae089/7693896 by KU Leuven Libraries user on 04 July 2024

Manuscript Doi: 10.1093/ecco-jcc/jjae089

1. Introduction

The incidence and prevalence of Crohn's disease [CD] is on the rise globally, with increases in incidence ranging from 4–15% yearly over the last three decades.[1] CD is a lifelong disease and optimal management is multidisciplinary and interprofessional and has become increasingly complex. Surgery is a major therapeutic avenue in this context. Indeed, half of patients with CD undergo one or more operations during their lifetime. Patients with CD often suffer from malnutrition, psychological comorbidities, and may have to accept and live with a stoma.[2-5] Many different medications and combinations thereof are reshaping clinical practice, while refined surgical techniques, tailored approaches, and a wider acceptance of a surgical alternative benefit patients. Hence, the best possible outcomes are currently achieved within dedicated expert centres providing personalized medicine.[6-10] The European Crohn's and Colitis Organisation [ECCO] provides an interdisciplinary framework with these evidence-based guidelines to inform and guide practice and clinicians caring for patients with CD. The present guidelines focus on surgery for CD, including pre- and perioperative aspects, and provides technical advice for a variety of common clinical presentations. Further, ECCO guidelines offer guidance on most aspects of interdisciplinary and interprofessional care for CD in separate publications.[11-16]

2. Methods

A detailed description of the methodology used is presented in the supplementary materials. This article is the second in a series of two publications on the ECCO evidence-based consensus on the management of CD. The first article covered medical management;[17] the present article is focused on surgical management while covering both medical and surgical management of perianal CD. These two articles together represent the evidence-based recommendations of the ECCO for CD and update prior guidelines published in 2020.[18,19] The present guidelines follow the GRADE methodology in terms of framing clinically relevant questions to draw evidence-based statements and recommendations. However, due to the peculiarities of the surgical literature, appraisal of the systematically researched literature was conducted according to the Oxford Centre for Evidence-Based Medicine, which grades from evidence level [EL]1: systematic review of randomized controlled trials to EL5: expert opinion.[20] This allowed us to formulate statements and practice recommendations that can effectively inform and guide clinical management.

Accepted Manuscript

Downloaded from https://academic.oup.com/ecco-jcc/advance-article/doi/10.1093/ecco-jcc/jjae089/7693896 by KU Leuven Libraries user on 04 July 2024

Manuscript Doi: 10.1093/ecco-jcc/jjae089

3. Perianal Crohn's disease

3.1. Medical approaches

Statement 3.1 ECCO CD Treatment GL [2024]

We do not recommend use of antibiotics as monotherapy for treatment of complex perianal fistulae in patients with CD [EL4]

Although antibiotics are widely used in the treatment of perianal CD, most available studies are uncontrolled.[21] To our knowledge, only one randomized controlled trial [RCT] compared placebo with antibiotics in perianal fistulae [supplementary table 1]. Remission at week 10 was observed in 1/8 [12.5%] versus 3/17 [17.6%] patients treated with placebo or antibiotics, respectively (relative risk [RR]: 1.41; 95% confidence interval [CI]: 0.17–11.54]. Complete healing was observed in 3/10 [30%] patients treated with ciprofloxacin and 0/8 patients treated with metronidazole.[22] Uncontrolled data and data from studies on combination therapy with anti-TNF suggest that ciprofloxacin can improve the efficacy of anti-TNF in the short term with good safety but with no impact on longer-term healing rates.[23,24] Importantly, despite the lack of evidence to support their role as monotherapy in closing perianal fistulae, antibiotics are indicated and recommended to treat and control perianal sepsis.

Statement 3.2 ECCO CD Treatment GL [2024]

We suggest against using thiopurines as monotherapy [azathioprine, mercaptopurine] for treatment of complex perianal fistulae in patients with CD [EL3]

The effect of azathioprine [AZA] on fistula healing in perianal CD has been numerically reported in RCTs in 18 patients only.[25-28] A meta-analysis on this limited group of patients demonstrated that AZA is not superior to placebo for fistula healing [RR: 2.00; 95% CI: 0.67–5.93].[29] Another study reported complete fistula closure in 9/29 [31%] fistulae during

Accepted Manuscript

Downloaded from https://academic.oup.com/ecco-jcc/advance-article/doi/10.1093/ecco-jcc/jjae089/7693896 by KU Leuven Libraries user on 04 July 2024

Manuscript Doi: 10.1093/ecco-jcc/jjae089

mercaptopurine therapy, in contrast to 1/17 [6%] with placebo-treated fistulae[30] [supplementary table 2]. Nevertheless, these data could not be incorporated in the pooled analysis, as they were reported as number of fistulae closing rather than number of patients who had complete fistulae closing. With the availability of effective anti-TNF agents, it seems inappropriate to recommend any further randomized placebo-controlled trial studying the efficacy of AZA in complex perianal fistulae.

Statement 3.3 ECCO CD Treatment GL [2024]

We recommend infliximab for the induction and maintenance of remission in complex perianal fistulae in CD [EL2]

Infliximab was the first agent shown to be effective in a RCT for inducing closure of perianal fistulae and for maintaining this response over 1 year. Complete response [defined as the absence of any draining fistulae at two consecutive visits at least 4 weeks apart] was observed in 4/31 [12.9%] placebo-treated patients versus 29/63 [46%] infliximab-treated patients [RR: 3.57; 95% CI: 1.38–9.25].[31] Subsequently, the ACCENT II trial evaluated the efficacy of infliximab [5 mg/kg every 8 weeks] in a maintenance trial in 195 patients who had a response [defined as a reduction of 50% of draining fistulae in two visits at least 4 weeks apart] at week 14 after open-label induction treatment with infliximab. A complete response was maintained until week 54 in 19/99 [19.2%] placebo-treated patients versus 33/96 [34.4%] infliximab-treated patients [RR: 1.79; 95% CI: 1.10– 2.92].[32] A recent meta-analysis of the existing data revealed that infliximab was effective in inducing [RR: 3.57; 95% CI:1.38–9.25] and maintaining clinical fistula healing [RR: 1.79; 95% CI:1.10–2.92] [33] with no significant risk of serious AEs as compared with placebo [RR: 1.31; 95% CI: 0.11–15.25, supplementary figure 1]. A combined evaluation of both RCTs for safety revealed a risk of serious AEs of 18.9% [33/175 patients] in the placebo groups versus 11.9% [24/201 patients] in the infliximab groups. Overall, the most recent meta-analysis (2023) provided low certainty on clinical outcomes. Some retrospective data suggest that fistula healing is more likely in patients with higher infliximab trough levels, suggesting the need for personalized dosing in this setting.[34-38]

Accepted Manuscript

Downloaded from https://academic.oup.com/ecco-jcc/advance-article/doi/10.1093/ecco-jcc/jjae089/7693896 by KU Leuven Libraries user on 04 July 2024

Manuscript Doi: 10.1093/ecco-jcc/jjae089

Statement 3.4 ECCO CD Treatment GL [2024]

We suggest use of adalimumab for induction and maintenance of remission in complex perianal fistulae in CD [EL3]

Fistula healing in the subgroup of patients with enterocutaneous or perianal fistulae [or both] at baseline [*n* = 117] was a secondary endpoint of the CHARM double-blind, placebo-controlled, randomized trial.[39] A subsequent post-hoc analysis that focused specifically on the efficacy of adalimumab over time in this subgroup confirmed the superiority of adalimumab over placebo [RR: 2.57; 95% CI: 1.13–5.84] for fistula healing after 56 weeks[39] [supplementary table 3]. Data from CHARM combined with data from the open-label extension study ADHERE revealed that there was no significant increase in serious AEs for patients treated with adalimumab [RR: 1.21; 95% CI: 0.43–3.38].[40-43] Data were insufficient to ascertain maintenance of fistula healing beyond 56 weeks, resolution of perianal sepsis, stoma-free survival, and quality of life. In a retrospective multicentre analysis evaluating 46 patients [83% with complex fistula] naïve to anti-TNF therapy, 72% of patients responded to adalimumab [54% remission, 18% partial response] at 6 months and 49% of patients maintained response at 12 months [41% remission, 8% partial response].[44] Additional data suggested that adalimumab may have a role in patients who failed infliximab because of immunogenicity [either primary non-responders or secondary loss-of-response]. The open-label CHOICE trial indeed demonstrated that complete fistula healing [mainly perianal fistula] could be achieved in 39% [34/88] of patients who initiated adalimumab after infliximab failure.[42] This finding has also been reported in a limited case series.[41] Some retrospective data suggest that fistula healing is more likely in patients with higher adalimumab trough levels, suggesting the need for personalized dosing in this setting.[35,37,40,45]

Statement 3.5 ECCO CD Treatment GL [2024]

There is insufficient evidence to recommend use of certolizumab pegol as a treatment for complex perianal fistulae in patients with CD [EL4]

Accepted Manuscript

Downloaded from https://academic.oup.com/ecco-jcc/advance-article/doi/10.1093/ecco-jcc/jjae089/7693896 by KU Leuven Libraries user on 04 July 2024

Manuscript Doi: 10.1093/ecco-jcc/jjae089

Certolizumab pegol [CZP], a pegylated humanized Fab' fragment that targets TNF-α, was evaluated for treatment of CD in two RCTs [PRECISE 1 and PRECISE 2]. The PRECISE 1 study included 662 patients with moderate-to-severe CD who were randomly assigned to receive either CZP 400 mg or placebo subcutaneously at weeks 0, 2, and 4, followed by administration every 4 weeks up to week 26.[46] Fistula closure was a secondary endpoint; 30% [14/46] of patients in the CZP group achieved closure versus 31% [19/61] in the placebo group. According to this study, CZP did not show a significant benefit for fistula closure.

The PRECISE 2 trial included 668 adults with moderate-to-severe CD[47] and used the same induction therapy as in PRECISE 1. Patients with clinical response [reduction of ≥100 from baseline score on the Crohn's disease activity index] were randomly assigned to receive CZP 400 mg or placebo every 4 weeks through week 26. Among patients responding to induction therapy with CZP, 28 of those randomized to CZP and 30 of those randomized to placebo had draining fistulae at baseline. The primary endpoint of the fistula subanalysis was fistula closure, defined as ≥50% closure at two consecutive post-baseline visits ≥3 weeks apart. At week 26, 54% [15/28] of CZP-treated patients achieved fistula closure [per protocol] compared with 43% [13/30] of placebo-treated patients; the difference was not statistically significant [$p = 0.069$]. At week 26, 36% of patients in the CZP group achieved complete fistula closure compared with 17% in the placebo group [$p = 0.038$]. Among patients who achieved the predefined criteria for fistula closure, there was a higher numerical proportion of patients who received continuous treatment with CZP compared with those who initially underwent induction therapy followed by placebo. However, these differences were not statistically significant for the small sample size analysed. Patients randomized to CZP in the maintenance phase maintained a 50% fistula closure rate at week 26 (11/15 [73%] patients vs 39% [5/15] patients; $p = 0.069$) and achieved 100% closure at week 26 (10/15 [67%] patients vs 4/13 [31%] patients; $p = 0.064$). The results from these post-hoc analyses suggest a possible effect of CZP in complex perianal fistulae in CD. However, possibly due to limited sample size, the benefit of CZP over placebo was not demonstrated.

Accepted Manuscript

Downloaded from https://academic.oup.com/ecco-jcc/advance-article/doi/10.1093/ecco-jcc/jjae089/7693896 by KU Leuven Libraries user on 04 July 2024

Manuscript Doi: 10.1093/ecco-jcc/jjae089

Statement 3.6 ECCO CD Treatment GL [2024]

There is insufficient evidence to recommend use of vedolizumab for the treatment of complex perianal fistulae in CD [EL4]

Vedolizumab [VDZ], a gut-selective α4β7 integrin antibody, was assessed for the treatment of complex perianal fistulae in an exploratory analysis of data from the GEMINI 2 study.[48] GEMINI 2 was a phase 3, randomized, double-blind, placebo-controlled trial that consisted of separate induction and maintenance phases. Following a 6-week induction period with VDZ, responders were randomly assigned to receive either placebo [VDZ/placebo group] or VDZ [VDZ/VDZ group] and entered a maintenance phase. Fistula closure was defined as the absence of clinically draining fistulae at weeks 14 and 52. A total of 57 patients with draining fistulae at the start of the maintenance period were included in the analysis; half of them previously failed anti-TNF therapy. By week 14, 28% [11/39] of patients in the VDZ/VDZ group and 11% [2/18] of patients in the VDZ/placebo group achieved fistula closure. However, in a meta-analysis, maintenance with VDZ did not reach statistical significance [RR: 2.54; 95% CI: 0.63–10.29; p = 0.19].[49] At week 52, 31% in the VDZ/VDZ group and 11% in VDZ/placebo group had fistula closure. Despite the numerically greater proportion of fistula healing observed in patients treated with VDZ, no statistically significant differences were observed. This post hoc analysis has several limitations, including a small sample size and inadequate statistical power. It is also biased by the induction phase with VDZ and lacks a design specifically evaluating VDZ for fistula closure.

A small clinical trial compared the efficacy of standard VDZ dosing versus standard dosing plus an additional dose at week 10 in patients with ≥1 draining perianal fistula at baseline.[50] Fistula closure was observed at week 30 in 12 [42.9%] patients (7 patients in the standard and 5 patients in the additional VDZ dose group).

In summary, the available evidence is of low quality and insufficient to recommend VDZ for complex perianal fistulae in patients with CD. However, VDZ could be considered in patients refractory or intolerant to anti-TNF therapy. Further studies with appropriate design are warranted to determine the benefit of VDZ in the treatment of complex perianal fistulae.

Accepted Manuscript

Downloaded from https://academic.oup.com/ecco-jcc/advance-article/doi/10.1093/ecco-jcc/jjae089/7693896 by KU Leuven Libraries user on 04 July 2024

Manuscript Doi: 10.1093/ecco-jcc/jjae089

Statement 3.7 ECCO CD Treatment GL [2024]

There is insufficient evidence to recommend use of ustekinumab as a treatment for complex perianal fistulae in CD [EL4]

The sole study comparing ustekinumab to placebo in treating complex perianal fistulae was a post hoc pooled analysis of data from the phase 2 CERTIFI and from the phase 3 UNITI-1 and UNITI-2 trials. This analysis provided information on the induction of fistula response and remission rates.[51] A total of 150 patients were treated with ustekinumab and 71 were treated with placebo. Due to the limited sample size, data from the final induction visit at week 8 were aggregated across the three studies for evaluation. The analysis revealed a higher proportion of fistula closure after 8 weeks of treatment in the ustekinumab group [24.7%] compared with the placebo group [14.1%], although the observed difference did not reach statistical significance [p = 0.073]. This finding was confirmed in a meta-analysis [RR: 1.77; 95% CI: 0.93–3.37].[49]

In the maintenance phase, fistula response to treatment was assessed at week 22 and 44. However, all patients included in the maintenance phase were either responders or non-responders to induction with ustekinumab who were re-randomized to receive ustekinumab or placebo, which may bias the results. Among patients in the maintenance phase, fistula response at week 22 occurred in 9/19 [47%] patients in the ustekinumab group and in 6/20 [30%] patients in the placebo group of the CERTIFI study and in 12/15 [80%] and 5/11 [45.5%] patients, respectively, at week 44 in the IM-UNITI study. Despite the numerically higher proportion of fistula healing in patients treated with ustekinumab, no significant differences were found. Moreover, being a post hoc analysis, fistula response or remission was a secondary outcome, making it an exploratory study with insufficient statistical power and a small sample size. In a recent meta-analysis that included 25 studies [most of which were observational studies and 20% of them being abstracts], 24.7% of patients achieved clinical remission of complex perianal fistulae at weeks 8–12 and 41.9% at 12 months.[52] Overall, there is insufficient evidence to recommend ustekinumab for treatment of complex perianal fistulae in patients with CD. However, ustekinumab could be considered in patients with perianal fistulae who are refractory or intolerant to anti-TNF agents. Further studies with appropriate design are warranted to determine the benefit of ustekinumab in the treatment of complex perianal fistulae.

Accepted Manuscript

Downloaded from https://academic.oup.com/ecco-jcc/advance-article/doi/10.1093/ecco-jcc/jjae089/7693896 by KU Leuven Libraries user on 04 July 2024

Manuscript Doi: 10.1093/ecco-jcc/jjae089

Statement 3.8 ECCO CD Treatment GL [2024]

There is insufficient evidence to recommend use of upadacitinib for the treatment of complex perianal fistulae in CD [EL4].

Upadacitinib [UPA] is currently the only JAK inhibitor approved for CD. Patients with moderate-to-severe CD were randomized to UPA 45 mg once daily or placebo for 12 weeks in two phase 3 induction trials. Patients who achieved clinical response after 12 weeks of UPA therapy were randomly assigned to receive UPA 30 mg or 15 mg or placebo once daily for 52 weeks. Among 1021 enrolled patients, 143 patients had fistulae at baseline [124 patients had perianal fistulae, 19 had enterocutaneous fistulae]. Post hoc analyses published as an abstract reported that in patients with draining fistulae at baseline, the proportion of patients with ≥50% reduction in draining fistulae at week 12 was significantly higher with UPA 45 mg compared with placebo (22/44 [50%] patients vs 3/22 [13.6%] patients; $p = 0.004$).

Furthermore, complete resolution of draining fistulae at week 12 was also significantly higher with UPA 45 mg than with placebo (21/44 [47.7%] patients vs 2/22 [9.1%] patients; $p = 0.002$). Numerically, a similar resolution pattern was seen in patients treated with either UPA 30 mg or 15 mg (1/11 [9.1%] and 3/17 [17.6%] patients, respectively vs 0/8 [0%] placebo-treated patients). Closure of the external fistula opening at week 52 was higher with either UPA 30 mg or 15 mg (4/19 [21.1%] and 6/35 [17.1%] patients, respectively vs 0/25 [0%] placebo-treated patients).[53] Nevertheless, this post hoc analysis has several limitations, including small sample size and inadequate statistical power.

In summary, the available evidence is of low quality and insufficient to recommend UPA as treatment for complex perianal fistulae in patients with CD. Further studies with appropriate design are warranted to determine the benefit of UPA in the treatment of complex perianal fistulae.

Accepted Manuscript

Downloaded from https://academic.oup.com/ecco-jcc/advance-article/doi/10.1093/ecco-jcc/jjae089/7693896 by KU Leuven Libraries user on 04 July 2024

Manuscript Doi: 10.1093/ecco-jcc/jjae089

Statement 3.9 ECCO CD Treatment GL [2024]

There is lack of evidence to recommend use of risankizumab for the treatment of complex perianal fistulae in CD [EL5]

3.2. Surgical techniques

Statement 3.10 ECCO CD Treatment GL [2024]

We recommend fistulotomy in carefully selected CD patients with a simple fistula in the absence of proctitis [EL4]

Studies on fistulotomy in CD are largely retrospective single-centre studies with specific eligibility criteria, including Parks classification superficial, intersphincteric, or low transsphincteric fistula,[54-60] absence of proctitis,[57,58] quiescent abdominal disease,[61] and a low number of daily bowel motions.[57] Few studies have compared the outcomes of fistulotomy in these select patients with alternative surgical procedures, which were mostly performed in patients with more complex or high anal fistulae. Due to this selection bias, these studies demonstrated improved healing and reduced recurrence rates in patients undergoing fistulotomy when compared with sphincter-preserving procedures, seton removal, and mesenchymal stem cells [MSC].[55,58,60]. In the largest studies, recurrence rates of 3–13% up to 1 year post-fistulotomy[55,57,58,60] were reported. However, few studies provide robust data on continence and wound healing. Other reports present data from heterogenous populations, including non-CD fistulae[54,59] or those undergoing multiple procedures prior to fistulotomy,[62] highlighting the difficulty in drawing recommendations from such data. Therefore, fistulotomy can only be recommended in simple, superficial, or low anal fistulae with absence of proctitis and stable intestinal disease.

Statement 3.11 ECCO CD Treatment GL [2024]

We suggest advancement flap as a treatment option for selected patients with CD and complex perianal fistulae in the absence of proctitis [EL4]

Accepted Manuscript

Downloaded from https://academic.oup.com/ecco-jcc/advance-article/doi/10.1093/ecco-jcc/jjae089/7693896 by KU Leuven Libraries user on 04 July 2024

Manuscript Doi: 10.1093/ecco-jcc/jjae089

Fistula closure can be achieved by raising a flap of mucosal tissue within the anus and lower part of the rectum. The advancement [AF] flap is then used to cover the internal opening of the fistula. CD patients with a single internal fistula opening and without proctitis or an anal stenosis are eligible. A systematic review identified 11 retrospective studies that reported data from 135 patients with CD perianal fistulae treated with an AF.[63] The pooled success rate was 66%. However, results were heterogeneous, probably due to varying definitions of success and length of follow-up. In a more recent meta-analysis, Stellingwerf et al. observed a weighted overall success rate of 61% in CD patients.[64] Results were not significantly different when compared with the success rate of ligation of the intersphincteric fistula tract [LIFT] procedure.

Additional prospective and retrospective series not included in the meta-analyses showed comparable clinical healing rates with AF, ranging from 47–90%[65-68] and recurrence rates around 15–20%. Two studies showed a higher clinical healing rate when AF was performed in patients treated with anti-TNF/immunomodulators [75.0% vs 37.5%] and after seton drainage.[68] One study also showed a 100% success rate in diverted patients.[66]

The disadvantage of AF is risk of impaired continence. The systematic review showed an acceptable postoperative incontinence rate, which was higher in AF when compared with the LIFT procedure [7.8% vs 1.6%].[64] However, most prospective series revealed a postoperative higher incontinence rate of up to 20% following AF. Conversely, one retrospective study reported a postoperative improvement in faecal continence.[68]

Statement 3.12 ECCO CD Treatment GL [2024]

We recommend ligation of the intersphincteric fistula tract as a treatment option for selected patients with CD and complex perianal fistulae [EL3]

LIFT aims to achieve fistula closure by ligation of the fistula tract in the intersphincteric plane, close to the internal opening. A theoretical advantage of LIFT over AF in CD patients is that it does not involve surgery of the [diseased] mucosa. Patients with a single, non-branching fistula and a well epithelialized tract are preferably eligible.

Two systematic reviews and meta-analyses, both including approximately 1300 patients, demonstrated a high clinical success rate of 77% and 69% [range 47–95%], respectively,

Accepted Manuscript

Downloaded from https://academic.oup.com/ecco-jcc/advance-article/doi/10.1093/ecco-jcc/jjae089/7693896 by KU Leuven Libraries user on 04 July 2024

Manuscript Doi: 10.1093/ecco-jcc/jjae089

after a median follow-up of over 1 year.[64,69] However, there was only a minority of patients with CD in these studies, and these patients had a lower success rate of 53%. Included studies were heterogeneous, with a wide range of outcomes and follow-up times, which makes it difficult to draw firm conclusions. The described recurrence rates were low [1.6%] and compared favourably to AF [7.8%].

Two retrospective and one prospective study published after the aforementioned meta-analyses reported results on an additional 95 patients with CD.[68,70,71] Clinical closure rates were comparable with the results previously published. However, data on recurrence were only reported in one series, with a rate of 21%.[70] Overall, this suggests a possible underreporting in the systematic reviews and meta-analyses. Another retrospective study demonstrated that in patients with a [predominantly] fibrotic tract after LIFT at MRI, no reinterventions or recurrences were seen during long-term follow-up, which also emphasizes the requirement of radiological healing to consider a patient healed.[68]

The only prospective series included 46 patients with a mean follow-up of 33 months and demonstrated fistula healing in 65% of patients.[71] Smoking at time of surgery was significantly associated with failure (hazard ratio [HR] 3.2), and a trend was seen towards increased failure in patients with active proctitis [HR 2.0]. No other factors [use of biologics, prior seton drainage, type of fistula, previous repair attempts] appeared to influence LIFT healing.

Postoperative complications after LIFT were seen in up to 14% of patients and were predominantly wound dehiscence. Incontinence rates appeared to be lower when compared with AF. However, continence should be interpreted with caution as there is a risk of under-reporting in the literature. The only retrospective series specifically examining postoperative incontinence in 37 patients demonstrated increased incontinence in 16% of patients after LIFT, whereas 53% of patients operated with LIFT and 43% with AF reported a postoperative improvement in faecal continence.[68]

Statement 3.13 ECCO CD Treatment GL [2024]

We recommend against the use of fibrin glue in the treatment of patients with complex perianal CD fistulae [EL4]

Accepted Manuscript

Downloaded from https://academic.oup.com/ecco-jcc/advance-article/doi/10.1093/ecco-jcc/jjae089/7693896 by KU Leuven Libraries user on 04 July 2024

Manuscript Doi: 10.1093/ecco-jcc/jjae089

Fibrin glue for treatment of perianal CD fistulae was assessed in an open-label RCT with 71 patients randomized to instillation of fibrin glue into the fistula tract or no further treatment after seton removal.[72] This RCT demonstrated a significant difference in overall clinical remission rate [38% for fibrin glue and 16% in the observation group; $p = 0.04$]. However, the length of follow-up in this RCT was only 8 weeks and was insufficient for a definitive judgement on the true success rate. The only retrospective series with adequate follow-up time [5 years] suggested an acceptable healing rate of 45% at 1 year,[73] but the single predictor for complete clinical remission was combination with medical therapy. This series also demonstrated a worrisome cumulative incidence of iterative anal surgery of 54% within 5 years, suggesting a high recurrence rate after fibrin glue. Despite the limited efficacy of fibrin glue in daily clinical practice, a uniform characteristic of all studies is the relatively good safety profile of this technique with no reported injury to the sphincter muscles.

Statement 3.14 ECCO CD Treatment GL [2024]

We recommend against anal fistula plug in the treatment of patients with complex perianal CD fistulae (EL4)

Use of a collagen anal fistula plug [AFP] in patients with perianal CD fistulae was assessed in a single RCT including 106 patients, which compared AFP after seton removal with seton removal only.[74] The fistula closure rate after 12 weeks in the AFP group was 33.3% in patients with complex fistulae and 30.7% in patients with simple fistulae as compared with 15.4% and 25.6% with seton removal alone, respectively. These differences were not statistically significant. In addition, there was a trend towards more adverse events [AE] in the AFP group [17% vs 8%; $p = 0.07$], although cumulative AE rates at 12 months follow-up were similar.

A systematic review of 12 observational studies including 84 patients with CD demonstrated an overall AFP success rate of 58%, with 14% recurrence after median follow-up of 9 [3–24] months.[75] However, there was no uniform definition for fistula closure or follow-up regimen. The quality of evidence for this systematic review was low due to risk of bias and imprecision. Use of an AFP in patients with CD appears to be relatively safe and may not affect continence [limited data on continence reported].[76] However, in studies using AFP for

Accepted Manuscript

Downloaded from https://academic.oup.com/ecco-jcc/advance-article/doi/10.1093/ecco-jcc/jjae089/7693896 by KU Leuven Libraries user on 04 July 2024

Manuscript Doi: 10.1093/ecco-jcc/jjae089

cryptoglandular fistulae, the abscess formation/sepsis rate ranged from 4–29% and the plug extrusion rate from 4–41%.[77]

Statement 3.15 ECCO CD Treatment GL [2024]

There is insufficient evidence to recommend use of video-assisted anal fistula treatment, fistula-tract laser closure, or over-the-scope clip for achieving healing in complex perianal fistulae in CD [EL5]

The role of video-assisted anal fistula treatment [VAAFT] in the treatment of anal fistulae in CD has been investigated only in small cohort studies. A first retrospective study including a mixed population of 84 patients with cryptoglandular and CD fistulae [*n* = 11] with a limited median follow-up of 8 months revealed a 27% healing rate in patients with CD.[78] Data on postoperative complications and risk of postoperative incontinence were lacking. A second retrospective study reported an overall healing rate of 82% at 9 months follow-up.[79] However, these results are difficult to interpret due to the very limited sample size of 11 patients and by the fact that internal opening closure was achieved by fashioning a rectal advancement mucosal flap. Furthermore, in about 40% of patients, faecal diversion [FD] was present at time of surgery. No patients experienced postoperative morbidity or postoperative faecal incontinence. VAAFT was further evaluated in a retrospective analysis of prospectively collected data of 25 patients with anal fistulae refractory to multiple previous surgeries and adequate medical treatment with biologics.[80] Twenty-one of 25 patients [84%] had a statistically significant improvement in a quality-of-life questionnaire before and 6 weeks after surgery, in particular in both pain and discharge scores. Eighty-one percent agreed that the procedure was the right decision and no patient regretted undergoing the procedure. Reoperation was necessary in one patient [4%].

Fistula-tract laser closure [FiLaC] is a relatively new sphincter-preserving technique initially reported in 2011. A systematic review published in 2022 identified six retrospective studies investigating FiLAC as a treatment option for perianal CD on a total of 50 patients.[81] There was heterogeneity in length of follow-up, fistula characteristics, and outcomes reported. The techniques used were only partially described, especially how to address internal opening[s] of the fistula, and included technical variations. The pooled rate of primary healing among

Accepted Manuscript

Downloaded from https://academic.oup.com/ecco-jcc/advance-article/doi/10.1093/ecco-jcc/jjae089/7693896 by KU Leuven Libraries user on 04 July 2024

Manuscript Doi: 10.1093/ecco-jcc/jjae089

the studies was 68% [95% CI: 53.0–84.0%]. No postoperative complications or faecal incontinence was observed, although not all studies reported these outcomes.

The role of over-the-scope clip [OTSC] in the treatment of anal fistulae in CD has only been investigated in several small observational case series, often with mixed populations; the majority were cryptoglandular cases and fewer were CD-related fistula. Mennigen et al. reported a case series of 10 patients including data on 6 patients with CD.[81] A total of 4/6 [66.7%] patients were on biologic therapy at the time of OTSC and all these patients achieved fistula closure; only 1 patient not receiving biologics healed. Although no postoperative morbidity or faecal incontinence was observed, the OTSC may be spontaneously passed [2/6, 33%] or need to be subsequently removed due to discomfort [1/6, 16.7%]. A study by Prosst and Joos reported OTSC in 100 patients (11 had inflammatory bowel disease [IBD]) with a closure rate of 45% in IBD.[82] Overall, the OTSC was spontaneously passed in 18 patients and appeared to be associated with a lower fistula closure rate of 33% [6/18 patients]. The OTSC needed to be removed or operatively explanted in 14 patients. No significant postoperative morbidity or faecal incontinence was reported. Although OTSC appears to be safe and may result in fistula closure in some patients, widespread adoption of this technique is currently limited by a paucity of data in CD.

Statement 3.16 ECCO CD Treatment GL [2024]

We recommend against use of chronic seton treatment as the sole treatment for perianal CD fistulae other than as palliation [EL3]

We recommend against a cutting seton due to the risk of incontinence [EL5]

There are no RCTs or studies comparing seton drainage with no treatment for perianal CD fistulae. Two systematic reviews, including 10 studies [*n* = 305 patients] on patients treated solely with seton drainage, reported varying results.[83,84] Complete closure rates ranged from 13.6–100% and recurrence rates from 0–83.3%. Timing of seton removal differed among studies [range 3 weeks to 40 months]. Included studies were prospective and retrospective cohort studies and case series and mostly of questionable quality.

Accepted Manuscript

Downloaded from https://academic.oup.com/ecco-jcc/advance-article/doi/10.1093/ecco-jcc/jjae089/7693896 by KU Leuven Libraries user on 04 July 2024

Manuscript Doi: 10.1093/ecco-jcc/jjae089

Additionally, the PISA trial published in 2020 compared the following three treatment strategies: long-term seton drainage alone, anti-TNF treatment, and surgical closure [the latter two with prior seton drainage].[85] The study was stopped by the data safety monitoring board because of futility. Seton treatment was associated with the highest reintervention rate [10/15 seton vs 6/15 anti-TNF vs 3/14 surgical closure patients; $p = 0.02$]. No substantial differences in perianal disease activity and quality of life were observed between the groups. Interestingly, in the accompanying PISA prospective registry, inferiority of chronic seton treatment was not observed for any of these outcome measures. This study suggested that chronic seton treatment should not be recommended as the sole treatment for perianal CD fistulae.

The cutting seton, in which a non-absorbable thread is inserted into the fistula tract and exteriorized through the anorectal canal with subsequent tightening, causing gradual cutting through the anal sphincter, should not be used as many studies have shown associated complications, including prolonged perianal pain and incontinence rates up to 58%.[84]

3.3. Combined approaches

Statement 3.17 ECCO CD Treatment GL [2024]

We recommend seton drainage preceding medical or surgical therapy for complex perianal CD fistulae [EL3]

Combined anti-TNF therapy and seton removal could result in improved healing rates, faster time to healing, longer time to relapse, and a reduced need for surgery than either therapy alone [EL3]

There were no RCTs comparing medical or surgical therapy with or without preceding seton drainage. Five systematic reviews were included.[83,84,86-88] Most studies focused on anti-TNF therapy. One of the largest systematic reviews [42 studies] included studies assessing anti-TNF agents for perianal fistulae. In most studies, anti-TNF was combined with preceding seton placement and it was suggested that combining seton drainage with an anti-TNF agent was superior. These results are consistent with another large systematic review that

Accepted Manuscript

Downloaded from https://academic.oup.com/ecco-jcc/advance-article/doi/10.1093/ecco-jcc/jjae089/7693896 by KU Leuven Libraries user on 04 July 2024

Manuscript Doi: 10.1093/ecco-jcc/jjae089

revealed that a combination of surgical treatment [including seton drainage] with medical therapy [anti-TNF agents and immunomodulators] may have additional benefit on healing of perianal CD fistulae compared with surgery or medical therapy alone.[88] One study showed that 75% of patients treated with anti-TNF therapy after prior seton placement healed compared with 63% of patients without initial seton.[89] Another study revealed that patients with seton placement prior to anti-TNF therapy had a better initial response [100% vs 82.6%; $p = 0.014$], lower recurrence rate [44% vs 79%; $p = 0.001$], and longer time to recurrence [13.5 vs 3.6 months; $p = 0.0001$] compared with patients receiving infliximab alone.[90] Additionally, patients with seton placement prior to anti-TNF therapy were less likely to require hospitalization and had reduced healthcare costs.[87] Studies have also shown shorter mean time to healing,[91,92] longer time to relapse,[92] and reduced need for repeat surgery[93] than with either therapy alone.

Timing of seton removal is largely variable and inconsistent between studies, ranging from 4–27 weeks post insertion.[93,94] However, the heterogeneity and low quality of the mainly retrospective studies included should be considered.

In most studies, seton drainage was performed prior to surgical closure in patients with perianal CD fistulae. However, several small retrospective studies showed no association between fistula healing rate after a LIFT procedure and prior seton placement or duration of seton drainage prior to surgery.[71,95]

A recent retrospective study analysed medical and surgical therapies to identify the optimal care strategy in 200 patients. Seton drainage prior to anti-TNF therapy alone did not significantly increase the fistula closure [HR: 1.15; 95% CI 0.61–2.32; $p = 0.66$]. The combination of seton placement and anti-TNF therapy followed by fistula closure surgery within 52 weeks was the best management strategy for fistula healing in multivariate analysis [$p = 0.02$]. Cumulative probabilities of fistula closure following the latter combined approach were 43.8%, 82.2%, and 93.7% at 1, 3, and 5 years, respectively. Patients concomitantly treated with a combination of anti-TNF therapy and immunosuppression at surgery had the highest long-term closure rate.[96]

Importantly, especially in case of perianal sepsis, adequate seton drainage seems to be of key importance to create optimal circumstances prior to starting medication or proceeding to surgical closure.

Accepted Manuscript

Downloaded from https://academic.oup.com/ecco-jcc/advance-article/doi/10.1093/ecco-jcc/jjae089/7693896 by KU Leuven Libraries user on 04 July 2024

Manuscript Doi: 10.1093/ecco-jcc/jjae089

Statement 3.18 ECCO CD Treatment GL [2024]

We recommend the combination of medical therapy with surgical fistula closure in amenable patients with complex perianal fistulae, as surgical closure results in improved long-term outcomes [EL3]

Two RCTs and one retrospective study investigated surgical closure of the fistula tract in combination with medical therapy. A first multicentre RCT compared seton removal and surgeon's choice of closure with seton removal alone in patients treated with adalimumab. There was no difference in clinical closure at 12 months [surgery 56.3% vs control 65.4%; $p = 0.48$] or in secondary outcomes measuring quality of life, continence, and AEs. Patients with surgical closure experienced longer disease duration and were more likely to have been previously treated with infliximab, suggesting more aggressive disease. Most patients [79%] were treated with fibrin glue with limited efficacy in perianal CD. In addition, the study was underpowered and robust conclusions could not be drawn from these data.[97]

Ninety-four patients were enrolled [38 patients with surgical closure and 56 with anti-TNF therapy] in the patient preference PISA II trial.[98] At 18 months, radiological healing was significantly more common after surgical closure (12/38 [32%] patients) than after anti-TNF therapy (5/56 [9%] patients) [$p = 0.005$]. Clinical closure was not significantly different between the two treatments [68% vs 52%, respectively; $p = 0.076$]. Fewer patients required a reintervention and the perianal disease activity index was significantly lower after surgical closure. Long-term results after a median follow-up of 5.7 years showed no recurrences in patients with radiological healing; recurrence was observed in 41% of patients with clinical closure without radiological healing.[99]

A retrospective study of 226 patients found no difference in healing when patients underwent a variety of surgeries alone compared with those undergoing surgery with concurrent infliximab [60% vs 59%, respectively]. Surgical procedures included seton drainage [50%], fistulotomy [41%], fibrin glue [6%], advancement flap [2%], and collagen plug [1%]. However, time to healing was 6.5 months after combination therapy [surgery and infliximab] and 12.1 months after surgery alone [$p < 0.0001$].[91]

Accepted Manuscript

Downloaded from https://academic.oup.com/ecco-jcc/advance-article/doi/10.1093/ecco-jcc/jjae089/7693896 by KU Leuven Libraries user on 04 July 2024

Manuscript Doi: 10.1093/ecco-jcc/jjae089

Statement 3.19 ECCO CD Treatment GL [2024]

There are conflicting data on allogenic adipose-derived stem cell therapy for the induction and maintenance of remission in complex perianal fistulae in CD [EL5]

The efficacy of MSC in treatment of perianal fistulae CD is mediated by anti-inflammatory properties and by the capacity to engraft and transdifferentiate into healthy tissue.[100] Allogenic MSC from adipose tissue (Cx601-darvadstrocel; Alofisel®) was assessed in a phase 3 RCT that included 212 patients with refractory fistulizing perianal CD.[101] At week 52, a significantly higher proportion of patients treated with darvadstrocel achieved combined remission when compared with controls [56.3% vs 38.6%; 95% CI 4.2–31.2; $p = 0.010$]. Combined remission was defined as closure of all treated external openings at clinical examination and absence of collections >2 cm at MRI. A study extension including 40 patients was prospectively conducted through week 104.[102] Clinical remission was reported in 14/25 [56%] patients in the darvadstrocel group and 6/15 [40%] patients in the control group, which was not statistically significant [95% CI: -15.5 to 47.5]. No serious AEs were reported at week 52 or week 104. Due to the high cost of darvadstrocel, the costs and potential benefits should be considered on a case-by-case basis of the clinical situation.

A meta-analysis published in 2018 that included three studies suggested that MSC of different origin significantly improved healing of perianal fistulae when compared with control at 6 to 24 weeks (odds ratio [OR]: 3.06; 95% CI: 1.05–8.90; $p = 0.04$) and numerically at 24 to 52 weeks [OR: 2.37; 95% CI: 0.90–6.25; $p = 0.08$].[103] No significant increases in AEs [OR: 1.07; 95% CI: 0.61–1.89; $p = 0.81$] were observed in treated patients. Limitations of the available studies on MSC in perianal CD include heterogeneity in protocols [allogenic or autologous MSC, bone-marrow or adipose tissue-derived MSC], low number of patients, varying definitions of fistula healing, and lack of consensus on definition of perianal fistula healing in MRI. Further studies based on robust well-defined radiological targets are needed to evaluate the role of MSC on the natural history of perianal fistulizing CD. Results from the phase 3 RCT ADMIRE-CD II will provide additional information.[104] Although the results of the ADMIRE-CD II were not yet published at the time of writing the present guidelines, the sponsor announced in a press release dated 17 October 2023 that the primary endpoint of combined remission at 24 weeks in complex perianal CD fistulae treated with darvadstrocel was not met. These inconclusive results were also presented at ECCO 2024 on 23 February 2024. The safety profile for darvadstrocel was consistent with prior studies and no new

Accepted Manuscript

Downloaded from https://academic.oup.com/ecco-jcc/advance-article/doi/10.1093/ecco-jcc/jjae089/7693896 by KU Leuven Libraries user on 04 July 2024

Manuscript Doi: 10.1093/ecco-jcc/jjae089

safety signals were identified. The final results of ADMIRE-CD II will help position this treatment in the management of complex perianal fistulae in CD.

Statement 3.20 ECCO CD Treatment GL [2024]

We suggest autologous adipose-derived stem cells may be used as a treatment option in complex perianal CD [EL4]

There is insufficient evidence to recommend use of platelet-derived factors or stromal vascular fraction in complex perianal CD [EL5]

Autologous stem cells [ASC] have the advantage of originating from the patient undergoing treatment, as opposed to donor-based therapy, thus making ASC readily available and less costly. ASC may be injected in a similar manner as allogenic MSC, mixed with fibrin glue, or loaded onto a fistula plug.

The most recent systematic review summarizing results of four RCTs demonstrated increased clinical healing rates of ASCs when compared with control patients treated with fibrin glue alone [OR: 3.19; 95% CI: 1.05–9.65; p = 0.04].[105] Unfortunately, it is difficult to draw firm conclusion for patients with CD, as only 20 patients with CD were included in these studies and most patients had a short follow-up of only 8 weeks. There are no studies that directly compared autologous to allogeneic stem cells for perianal CD fistulae.

The best evidence on the use of ASCs for perianal CD fistulae comes from various prospective case series including a total of 110 patients.[106-111] Although treatment protocols varied substantially, most involved curettage of the fistula tract, suturing of the internal opening [with or without an advancement flap], and filling of the fistula tract with ASCs. Most studies allowed a second injection of ASCs in patients with incomplete closure. Clinical healing rates, defined as no suppuration from the external orifices, ranged from 33–91%. However, most of these series lacked an adequate follow-up [range 2–12 months] with recurrence rates rarely described. The largest study included 30 patients and showed a closure rate of 83.3% with a recurrence rate of 33%.[110]

Accepted Manuscript

Downloaded from https://academic.oup.com/ecco-jcc/advance-article/doi/10.1093/ecco-jcc/jjae089/7693896 by KU Leuven Libraries user on 04 July 2024

Manuscript Doi: 10.1093/ecco-jcc/jjae089

Despite the additional requirement of harvesting cells via liposuction to obtain ASC, the procedure appeared safe. The most common AEs were postoperative pain, abscess, or bleeding.[105] There were no significant differences in AEs when compared with the control group [OR: 1.06; 95% CI: 0.71–1.59; p = 0.77].

There are also some studies that investigated the effects of injecting freshly collected microfragmented autologous adipose tissue, platelet-derived growth factors, or stromal vascular fraction into perianal CD fistulae.[109,111,112] Feasibility was demonstrated in most patients and results appeared comparable to ASCs, with clinical healing ranging from 38–67%. Harvesting, preparation, and administration of these tissues are described as easy, inexpensive procedures with minimal AEs. Again, these series suffer from small patient numbers and brief follow-up and lack description of recurrence rates. Further studies are required to define the true potential of these approaches.

Statement 3.21 ECCO CD Treatment GL [2024]

We suggest medical treatment in anogenital and rectogenital CD fistulae and counselling for surgical closure in selected patients with CD [EL5]

Anogenital and rectogenital fistula are complex and disabling conditions that are better managed by an experienced multidisciplinary team. No RCTs or prospective studies were found that compared anti-TNF agents alone versus anti-TNF agents and surgery combined to treat these fistulae.

A post hoc analysis of the ACCENT II study identified 25 women with ano- or rectovaginal fistulae.[113] This study demonstrated that infliximab is more effective than placebo in prolonged closure [defined as non-draining fistula at week 14]; 13/29 [44.8%] fistulae responded to induction regimen with infliximab and were closed. From weeks 14 to 46, among responders in the infliximab maintenance group, the proportion of rectovaginal fistulae that closed ranged from 54.5–90.0% compared with 28.6– 42.9% in the placebo group.

A French retrospective multicentric observational study including 131 consecutive patients treated with anti-TNF agents for 1 year found that 37% of patients had complete clinical fistula closure, 22% had partial response, and 41% had no response.[114] Complementary

Accepted Manuscript

Downloaded from https://academic.oup.com/ecco-jcc/advance-article/doi/10.1093/ecco-jcc/jjae089/7693896 by KU Leuven Libraries user on 04 July 2024

Manuscript Doi: 10.1093/ecco-jcc/jjae089

surgery was allowed, including advancement flap [rectal, vaginal, or Martius flap], fibrin glue, collagen plug, or gracilis muscle interposition and performed during the first year in 10 patients [8%], translating into a higher closure rate in multivariate analysis [adjusted RR: 2.02; 95% CI 1.25–3.26; *p* = 0.004]. A retrospective study of 166 patients who underwent operations for anogenital fistulae revealed an overall fistula healing rate of 71.7% [*n* = 119] with a median follow-up of 5.5 [1.2–9.8] years.[115] Nearly one-third of patients [33.1%] achieved complete healing after first surgery, 51.8% [*n* =86] after the second, and 62.1% [*n* = 103] after the third operation.

A recent systematic review found nine studies that reported healing, success, or closure [range 14–81%] across multiple surgical procedures; seven studies reported success rates ranging from 50–75%.[116] However, those studies were of low quality and had limited sample sizes, various concomitant medical therapies, heterogenous fistula and patient characteristics, outcomes considered, and definition of outcomes.

Statement 3.22 ECCO CD Treatment GL [2024]

We suggest faecal diversion with a defunctioning ileostomy or colostomy for treatment of refractory, complex perianal CD [EL4]

Patients with treatment-refractory perianal CD may benefit from faecal diversion [FD] with a diverting ileostomy or colostomy. Indeed, FD is associated with a high early clinical response rate and an improved quality of life, although FD often becomes permanent. A systematic review of 16 retrospective studies with 556 patients with perianal CD found that FD is associated with early clinical response in 63.8% [95% CI: 54.1–72.5%].[117] However, stomas were often permanent and only 16.6% [95% CI: 11.8–22.2%] of patients ultimately had successful ostomy reversal. The rate of proctectomy after failure of temporary diversion was 41.6% [95% CI: 32.6– 51.2%]. Proctitis was associated with increased risk of permanent diversion.

One study compared FD plus local procedures for perianal CD [*n* = 13] to local procedure without FD [*n* = 26].[118] Complete resolution of perianal CD was observed in 11 [85%] patients with FD versus 5 [19%] patients without FD. Of the FD patients, 6 [46%] had stoma reversal, of whom 3 [50%] remained disease free, 1 [17%] required successful additional

Accepted Manuscript

Downloaded from https://academic.oup.com/ecco-jcc/advance-article/doi/10.1093/ecco-jcc/jjae089/7693896 by KU Leuven Libraries user on 04 July 2024

Manuscript Doi: 10.1093/ecco-jcc/jjae089

local procedures, and 2 [33%, 15% overall] required re-diversion. Thus only 4/13 [31%] of FD patients ultimately had stoma reversal. Another study of 21 patients showed that although some patients may achieve complete healing, many do not; initial improvement was followed by plateau in 7 [33%], temporary improvement in 6 [29%], no effect in 4 [19%], and healing in 4 [19%] patients.[119] In this study, 11 [52%] patients subsequently had proctocolectomy, 6 [28.6%] had their stoma in situ, and 4 [19%] had stoma reversal. In a large series of 138 patients who had initial FD, a total of 63 [45%] underwent subsequent total proctocolectomy, 45 [33%] had their stoma without proctectomy, and 30 [22%] had stoma reversal.[120] Independent predictors of lack of stoma reversal included proctitis [OR: 7.5; 95% CI: 2.4–33.4], 1–2 seton placements [OR: 3.3; 95% CI: 1.4–8.8], and >2 seton placements [OR: 6.9; 95% CI: 1.2–132.5]. Biologics were not associated with stoma closure [$p = 0.25$].

Few studies examined quality of life before and after FD in perianal CD. In a series of 34 patients with FD, compared with similar patients without FD, patients with FD had fewer perianal CD symptoms [44% vs 79%; $p < 0.05$], higher Gastrointestinal Quality of Life index scores [68 vs 62 points; $p < 0.001$], and higher GI symptoms sub-scores [81 vs 67; $p < 0.0001$] compared with non-diverted patients.[121] The most recent meta-analysis evaluating 1578 patients managed in the biologic era similarly concluded that FD improved symptoms and quality of life, while bowel continuity could be successfully restored in a quarter of the patients.[122]

Statement 3.23 ECCO CD Treatment GL [2024]

We suggest proctectomy for treatment of refractory, complex perianal CD despite defunctioning stoma [EL4]

Proctectomy may be recommended in many patients with perianal CD. However, proctectomy is associated with a substantial risk of a non-healing perineal wound in the short-term and a risk of colonic or small-bowel recurrence in the long-term. In a series of 127 patients with perianal CD, proctectomy was required in 32 [25.2%] patients.[123] Several studies discussed independent risk factors for proctectomy, including age at first perianal fistula [$p < 0.02$], perianal fistula at the time of CD diagnosis [$p < 0.04$], >3 fistulae during

Accepted Manuscript

Downloaded from https://academic.oup.com/ecco-jcc/advance-article/doi/10.1093/ecco-jcc/jjae089/7693896 by KU Leuven Libraries user on 04 July 2024

follow-up [$p < 0.01$], and proctitis [$p < 0.0001$].[124] Other studies also reported malignancy in the setting of perianal CD as an indication for an oncologic proctectomy.[124-126]

Proctectomy for perianal CD is typically performed as an abdominoperineal resection [APR] with a colostomy or as a total proctocolectomy with end-ileostomy in case of extensive colonic involvement.[123-128] In terms of extent of bowel resection in the setting of perianal CD, a single study examined APR with colostomy and reported a clinical recurrence rate of colonic CD of 22% for an endoscopic colonic recurrence rate of 29%; overall 5% of patients required completion total colectomy.[128] It is important to note that proctocolectomy does not cure CD; a multicentre retrospective study of total proctocolectomy with end-ileostomy including 193 patients with refractory perianal CD reported a 23% small-bowel recurrence within 2 years.[127] Independent risk factors for recurrence included CD diagnosis at age <18 years [HR: 2.56; 95% CI: 1.40–4.71] and previous small-bowel resection [HR: 2.61; 95% CI: 1.42–4.81].

Proctectomy for IBD is often performed as an inter-sphincteric dissection, limiting the size of the perineal incision.[123-128] The inter-sphincteric groove may not be identifiable due to scarring in up to 78% of patients with perianal CD, limiting the ability to perform an inter-sphincteric dissection and impacting wound healing.[126] Indeed, delayed perineal wound healing is often observed after proctectomy in perianal CD.[125,129-132] When wounds are left open to heal by secondary intention, an uncommon practice nowadays, only 58% of perineal wounds of patients with IBD were healed after 6 months of dressing changes.[130] Wound irrigation has also been explored in the 1980s and half of perineal CD wounds were healed at 30 days compared with 87% after APR for cancer in the absence of radiotherapy.[132] Male gender was a risk factor for delayed healing, especially when the drain exited through the wound instead of laterally. Higher success rates were observed when myocutaneous flaps were used, although patients are still at risk for subsequent fistulization [20% in a small study].[131] In a large series of 126 patients, 72 [53%] wounds were healed at 12 weeks, while delayed healing was observed in 35 [26%] and non-healing in 29 [21%] patients.[125] Preoperative perianal sepsis was an independent predictor of a delayed- or non-healing wound [$p = 0.001$], suggesting FD prior to proctectomy.[129] For non-healing perineal wounds with metastatic CD, hyperbaric oxygen therapy may be an option.[133]

Accepted Manuscript

Downloaded from https://academic.oup.com/ecco-jcc/advance-article/doi/10.1093/ecco-jcc/jjae089/7693896 by KU Leuven Libraries user on 04 July 2024

Manuscript Doi: 10.1093/ecco-jcc/jjae089

Practice Points

Fistula treatment should start with insertion of a seton followed by medical treatment [preferably anti-TNF]. In the absence of proctitis, patients should be counselled for surgical closure.

Perianal fistulae in CD can have a substantial detrimental impact on patient quality of life. Current biological understanding of perianal fistulizing CD remains inadequate and previous classification systems have not provided clear guidance on therapy in clinical practice. A new classification presented in Figure 1 identifies four groups of patients.[134] Key elements include stratification according to disease severity and desired outcome. This classification can guide patients and clinicians in decision making on a 'treat to patient goal basis' by a combined medical and surgical approach.

All treatment should start with insertion of a seton to control sepsis and create a patent tract, followed by medical treatment [preferably anti-TNF with high trough level]. After good response to anti-TNF therapy, seton removal can be considered within 2–8 weeks to aim for closure with medication only.[135] Although clinical closure can be achieved in up to 60% by medication, it should be noted that MRI closure is rare [<10%] with high risk of recurrence and surgical reintervention.[98] MRI closure is more frequently seen after surgical closure under anti-TNF therapy [up to 40%], with no recurrences after long-term follow-up in case of a completely fibrotic tract on MRI.[99] Therefore, in absence of proctitis, amenable patients should be counselled for surgical closure. For patients with an inter-sphincteric or low trans-sphincteric single fistula tract, fistulotomy can be considered as this procedure will have the highest success rate.

In case of complex perianal fistulae, AF or LIFT can be offered, depending on fistula characteristics. Stem cells can be an alternative, especially in patients with multiple internal openings or pre-existing complaints of incontinence.

In case of anti-TNF failure and surgically refractory fistulae, more experimental approaches [such as hyperbaric oxygen therapy or new medical approaches] can be attempted, ideally in the context of a prospective clinical trial. An algorithm to guide the management of perianal CD is illustrated in Figure 2.

Downloaded from https://academic.oup.com/ecco-jcc/advance-article/doi/10.1093/ecco-jcc/jjae089/7693896 by KU Leuven Libraries user on 04 July 2024

Manuscript Doi: 10.1093/ecco-jcc/jjae089

4. Surgical management of abdominal Crohn's disease

4.1 Preoperative optimization

Statement 4.1 ECCO CD Treatment GL [2024]

We recommend elective bowel resection over emergency surgery in patients with CD [EL2]

A meta-analysis of cohort series including 75'971 CD patients from 15 countries reported a significantly lower mortality among patients who underwent elective [0.6%; 95% CI: 0.2%-1.7%] vs emergent surgery [3.6%; 95% CI: 1.8%-6.9%], highlighting the importance of perioperative optimization and avoidance whenever possible of emergent surgeries[136].

Statement 4.2 ECCO CD Treatment GL [2024]

Pre-operative optimization should be initiated, followed by re-assessment of the patient for surgical intervention [EL3]

A recent meta-analysis showed that emergency bowel resection is associated with a higher risk of overall postoperative complications and abdominal septic complications.[137] This is consistent with a European Society of Coloproctology prospective snapshot audit in which emergency surgical intervention was associated with unfavourable postoperative outcome.[138] Another recent multicentre international observational study concluded that emergency intervention in patients with an abdominal abscess increased the risk of postoperative complications and abscess recurrence.[139] Moreover, patients undergoing emergency surgery for CD have a higher rate of stoma formation.[140,141] Lastly, laparoscopic surgery in the emergency setting has a higher conversion rate and involves resection of longer segments of small bowel, which is a concern in CD due to a lifetime risk of short bowel.[140]

The drivers behind these unfavourable outcomes may be patient status and the environment of care typical of an emergency situation. Emergency resection [within 48 hours of admission] is performed on tissue characterized by profuse oedema and acute inflammation in a patient often in an unstable condition by a team that may not be specialized in IBD or even colorectal surgery. Patients with CD who undergo emergency operation typically have

Accepted Manuscript

Downloaded from https://academic.oup.com/ecco-jcc/advance-article/doi/10.1093/ecco-jcc/jjae089/7693896 by KU Leuven Libraries user on 04 July 2024

Manuscript Doi: 10.1093/ecco-jcc/jjae089

a severe form of disease, are malnourished, and are often on steroids, immunomodulators, biologicals, or combinations thereof with a higher likelihood of undrained abscesses, fistulae, or both at time of emergency surgery. Drainage of an abscess and relieving obstruction together with preoperative optimization should be initiated immediately on admission, as described in recent prospective cohort series[142,143] and advised in ECCO topical reviews.[144,145]

Preoperative optimization of an emergency CD patient and transfer of care from the acute to the specialized/elective setting is key to improving short- and long-term postoperative outcomes. On the other hand, free bowel perforation is one of the few situations where urgent surgery may be mandatory as bowel perforation is a very rare but serious and potentially life-threatening complication in CD. The literature is characterized by low-quality, heterogenous studies based on historical data. A study from Korea estimated the incidence to be 2.15% in the Korean CD population.

There are two important points to consider when CD leads to bowel perforation.

1. Bowel-wall thickness: Bowel-wall thickening in CD occurs due to chronic inflammation and scarring and differs from ischaemic bowel perforation, which occurs when there is a decreased blood supply to the bowel, potentially resulting in a perforation. Symptoms, diagnostic approach, and treatment may also differ between these conditions.
2. Size of perforation: Bowel perforation in CD can vary in size and presentation. While some cases may involve small or microscopic perforations, others can present as larger perforations. Timely diagnosis and appropriate treatment can prevent further complications and improve outcomes.

A small-bowel perforation can, in very selected situations and under supervision of an experienced colorectal surgeon, be managed conservatively. This mandates a very close clinical follow-up and the capacity to operate immediately should the patient deteriorate. The early involvement of a multidisciplinary team consisting of an IBD gastroenterologist, an IBD surgeon, a radiologist, and a dietician is mandatory in emergency presentation of CD due to the complexity of the disease and management.

Statement 4.3 ECCO CD Treatment GL [2024]

We recommend control of sepsis prior to abdominal surgery for CD [EL3]

Accepted Manuscript

Downloaded from https://academic.oup.com/ecco-jcc/advance-article/doi/10.1093/ecco-jcc/jjae089/7693896 by KU Leuven Libraries user on 04 July 2024

Manuscript Doi: 10.1093/ecco-jcc/jjae089

Statement 4.4 ECCO CD Treatment GL [2024]

We suggest use of intravenous antibiotics and percutaneous image-guided drainage as the first-line treatment for intra-abdominal abscesses related to CD [EL3]

Statement 4.5 ECCO CD Treatment GL [2024]

We suggest conservative treatment following successful percutaneous image-guided drainage of an intra-abdominal abscess in carefully selected cases. A low threshold for surgery is recommended in the event of medically refractory cases [EL4].

Penetrating CD complicated by intra-abdominal abscesses [IASC] represents a complex condition requiring involvement of interventional radiologists, gastroenterologists, and surgeons. An [elective] operative approach appears indicated in most patients, as conservative management leads to complete abscess resolution in less than 30% of selected cases, while delayed elective surgery is associated with improved postoperative outcomes, avoidance of a stoma, and abscess recurrence.[146,147 148]

Observational studies indicate that failure to control IASC preoperatively increases the risk of postoperative complications, anastomotic leaks, postoperative sepsis, and stoma formation, resulting in an increased length of hospital stay.[139,149-151] Percutaneous drainage [PD] under ultrasonographic or CT guidance may be the primary approach for treatment of well-defined abscesses. Successful drainage rates of 74–100%, allowing avoidance of emergency surgery in 14–85% of patients, were reported.[18] PD with antibiotics to control IASC resulted in better quality of life than surgery alone, provided abscesses were completely drained.[139,149,152] PD and antibiotic therapy should be combined with perioperative optimization, including nutritional support and stopping or decreasing corticosteroids. Despite PD, these patients still present with higher morbidity than those without preoperative IASC.[140]

It is worth noting that when performed by specialized high-volume IBD surgeons, early laparoscopic surgery [<1 week after admission] was safe, feasible, and associated with similar morbidity rates when compared with delayed surgery [within 3 weeks after initial admission, including PD in 28% of patients].[153] However, steroid treatment before PD and short waiting interval [<2 weeks] were associated with a higher risk of abscess recurrence, while anaemia and long waiting interval [>4 weeks] increased the risk of stoma construction.[153] Overall, performing surgery 2–4 weeks after successful PD was associated

Accepted Manuscript

Downloaded from https://academic.oup.com/ecco-jcc/advance-article/doi/10.1093/ecco-jcc/jjae089/7693896 by KU Leuven Libraries user on 04 July 2024

Manuscript Doi: 10.1093/ecco-jcc/jjae089

with the lowest risk of postoperative IASC.[139] Identifying patients who may be treated without surgery is challenging and currently relies on clinical judgment rather than on evidence. In general, medically refractory disease, presence of stenosis, or an enterocutaneous fistula represent clear indications for surgery.[152]

Statement 4.6 ECCO CD Treatment GL [2024]

We recommend endoscopic balloon dilatation as a treatment option for small-bowel strictures <5 cm in length when technical expertise is available [EL2]

In a review of 1463 patients with CD who underwent 3213 endoscopic balloon dilatation [EBD] procedures, a stricture length <5 cm was mostly amenable to EBD and associated with a surgery-free outcome; every additional centimetre in stricture length increased the need for surgery by 8% [p = 0.008].[154] This is consistent with other reviews.[155-157] Inflammation, disease activity, type of stricture, balloon diameter, and duration of inflation did not affect outcomes.[154,156]

While therapeutic success can be achieved after a single dilation, several dilations may be necessary to resolve obstructive symptoms; however, repeat dilation may reduce quality of life.[158,159] Although accessory endoscopic techniques, including local steroid injection, cutting procedures [e.g. Argon beaming], and stent implantation have been proposed to improve resolution,[154] the evidence is weak. Some retrospective cohort studies suggested that combined therapy with anti-TNF and EBD may prevent intestinal stricture recurrence and surgery in hospitalized patients with CD.[160,161]

An unresolved controversy is the dilation efficacy of primary versus anastomotic strictures. Identification of predictive factors for the long-term success of EBD may assist clinical decision making and an individualized treatment approach in stricturing CD.[162]

In conclusion, short-term therapeutic success of EBD is high in a selected group of patients when technical expertise is available. However, the impact on long-term quality of life, need for repeat dilations, and strictureplasty or bowel resection is less clear.

Practice point

Whenever possible, elective surgery is preferable to an emergency procedure in both fistulizing and obstructive CD. The control of IASC is multidisciplinary and draws from interventional radiology, infectious disease, gastroenterology, and surgery. Imaging [sonography, CT, MRI], swift drainage, antibiotics, intensified perioperative therapy, and specialist care are the mainstays of treatment. PD is mostly a bridge intervention rather than

Accepted Manuscript

Downloaded from https://academic.oup.com/ecco-jcc/advance-article/doi/10.1093/ecco-jcc/jjae089/7693896 by KU Leuven Libraries user on 04 July 2024

Manuscript Doi: 10.1093/ecco-jcc/jjae089

a definitive solution; elective surgery performed 2-4 weeks thereafter minimizes postoperative complications and need for a stoma.

Primary conservative management of bowel obstruction includes rehydration, nasogastric decompression, imaging, and consideration of high-dose steroid therapy. Frequent monitoring and surgical consultation are critical. Surgery can be deferred in most cases but should be considered during follow-up. Definitive non-surgical management may be successful but must be carefully balanced and discussed with the individual patient.

Statement 4.7 ECCO CD Treatment GL [2024]
We recommend preoperative nutritional assessment and identification of nutritional risk by IBD-dedicated dietitians for patients with CD who need surgery [EL2]

Statement 4.8 ECCO CD Treatment GL [2024]
When feasible, enteral nutrition should be the strategy of choice for preoperative optimization in patients with CD [EL3]

Malnutrition is common in patients with CD requiring surgery and is a risk factor for adverse postoperative outcomes and complications. Systematic nutritional risk screening [body mass index, unintentional weight loss, reduced dietary intake,
illness severity] together with perioperative nutritional support may mitigate the perioperative risks associated with malnutrition. An ECCO consensus and topical review on perioperative dietary therapy in CD concluded than exclusive enteral nutrition [EEN] represented a valid preoperative optimization strategy for reducing complications and improving nutritional status in patients with CD, likely by modulating inflammatory status and improving microbial composition.[145,163-165]

The benefits of preoperative EEN have been consistently reported, leading to a marked reduction of postoperative morbidity [21.9% vs 73.2%; OR: 0.09; 95% CI: 0.06–0.13; $p < 0.01$], although data on biochemical optimization are still debatable.[166-168] Conversely, the role of parenteral nutrition [PN] in the preoperative optimization strategy is more debated.[169] Importantly, EEN requires dedicated nutritional support and high patient compliance to be successful.

Accepted Manuscript

Downloaded from https://academic.oup.com/ecco-jcc/advance-article/doi/10.1093/ecco-jcc/jjae089/7693896 by KU Leuven Libraries user on 04 July 2024

Manuscript Doi: 10.1093/ecco-jcc/jjae089

The use of PN in the perioperative period should be reserved for patients unable to tolerate EEN, do not meet their nutritional requirements with EEN, or in which EEN is contraindicated.[170] In a recent prospective multicentric cohort study, preoperative EEN reduced morbidity for infection and temporary stoma requirement in malnourished patients with CD [164] . In another recent cohort study, patients receiving preoperative PN had significantly lower rates of non-infectious complications [OR: 0.07; 95% CI: 0.01–0.80; p = 0.03]. A subset of frail patients with severe CD who did not tolerate EEN and required PN presented a similarly high rate of IASC and primary stoma as when upfront surgery was elected. Hence, the advantage of providing PN to this subgroup of frail patients is questionable, as these patients may benefit from an early surgical approach followed by nutritional replacement.[171] Therefore, early surgery with postoperative optimization may be considered in frail, severely ill patients who do not tolerate EEN and accept a diverting stoma.

Statement 4.9 ECCO CD Treatment GL [2024]

We recommend that steroids should be tapered whenever possible before surgery to reduce the risk of complications [EL2]

Previous ECCO guidelines have reported that treatment with >20 mg prednisolone daily for >6 weeks increases the risk of postoperative septic complications.[11,18,172] Whilst there is no large RCT confirming this position, one large multicentre cohort study and numerous retrospective cohort studies have identified this risk [summarized in 3 meta-analyses].[173-175] Indeed, preoperative steroid use was a significant risk factor for major complications, including an overall increased risk of postoperative complications [OR: 1.41; 95% CI: 1.07–1.87] and a specifically increased risk of postoperative IASC [OR: 1.68; 95% CI: 1.24–2.28].[174,176] Patients who received >40 mg perioperative oral steroids had the highest risk of overall complications [OR: 2.04; 95% CI: 1.28–3.26]. A meta-analysis confirmed an almost doubling of total wound infections [OR: 1.70; 95% CI: 1.38–2.09].[173] Similar to the results from the large multicentre cohort study, an increased risk for anastomotic leak was also observed [OR: 1.51; 95% CI: 1.02–2.25].[175]

Steroids should be reduced before surgery as part of a preoperative optimization strategy in combination with nutritional optimization and drainage of sepsis. If this is not possible, consideration should be given to a staged procedure with a temporary stoma.

Accepted Manuscript

Downloaded from https://academic.oup.com/ecco-jcc/advance-article/doi/10.1093/ecco-jcc/jjae089/7693896 by KU Leuven Libraries user on 04 July 2024

Manuscript Doi: 10.1093/ecco-jcc/jjae089

Statement 4.10 ECCO CD Treatment GL [2024]

We recommend against cessation of biologics prior to surgery as current evidence suggests that preoperative treatment with anti-TNF therapy [EL3], vedolizumab [EL3], and ustekinumab [EL4] does not increase the risk of postoperative complications in patients with CD undergoing abdominal surgery

Anti-TNF therapy

Use of biologicals in patients with CD undergoing surgery remains controversial. Concern exists over the desired modulation of the immune response and the potential to increase postoperative complications. Several retrospective studies regarding anti-TNF agents have been published over the last 20 years. Some suggested an increased incidence of complications in patients receiving anti-TNF agents preoperatively and other studies showed no difference. Several meta-analyses have also reported varying conclusions.[177] Several prospective studies also reached inconsistent conclusions. This variation probably represents heterogenous populations, different outcomes, and inconsistent definitions of outcomes. Most evidence is concentrated on infliximab and adalimumab.[177] The PUCCINI trial is the largest prospective trial to date and revealed no difference in the rate of any infection between patients using biological therapy and those not.[178] Detectable preoperative serum concentrations of anti-TNF agents also did not increase the risk of surgical site or overall infection rates.[178] Hence, anti-TNF therapy can be continued prior to surgery.

Vedolizumab

Although initial retrospective data suggest that VDZ leads to an increased risk of postoperative infection, subsequent studies showed no increased risk. These data were confirmed by most, but not all, recent meta-analyses.[179-182] The latest of these showed no significant differences in overall complications [OR: 1.04; 95% CI: 0.48–2.24],[180] infectious complications [OR: 1.00; 95% CI: 0.37–2.69], or surgical site infections [OR: 1.45; 95% CI: 0.33–6.32] for those receiving VDZ preoperatively. Therefore, VDZ can be continued prior to surgery.

Ustekinumab

Although one meta-analysis focused on ustekinumab and postoperative complications, the comparator was patients receiving anti-TNF therapy.[183] No difference in complications and infectious complications were identified. The only cohort study comparing ustekinumab with

Accepted Manuscript

Downloaded from https://academic.oup.com/ecco-jcc/advance-article/doi/10.1093/ecco-jcc/jjae089/7693896 by KU Leuven Libraries user on 04 July 2024

Manuscript Doi: 10.1093/ecco-jcc/jjae089

non-biological therapy revealed that preoperative use of ustekinumab is an independent risk factor for intra-abdominal sepsis [OR: 2.93; 95% CI: 1.16–7.40; p = 0.02].[184] Although further studies are required to confirm the safety of ustekinumab and surgery, current data suggest that cessation before surgery may not be necessary.

There is no available evidence of the possible impact of preoperative use of CZP, rizankizumab, or JAK inhibitors on postoperative morbidity in patients with CD undergoing abdominal surgery. The safety of continuing newer biological agents prior to surgery remains unknown.

Practice points

Preoperative optimization is a key element in successful management of complex situations and chronic disease. Many aspects of optimal perioperative care are generic and common to all abdominal procedures,[185] although some aspects are particularly important in the context of CD [venous thromboembolism prophylaxis, nutrition, iron management, drug management, minimally invasive approaches, and bowel- and sphincter-sparing techniques].[186,187] While high-dose steroids should be tapered to reduce surgical morbidity, current biological therapy can safely be continued perioperatively.

4.1 Surgical techniques

Statement 4.11 ECCO CD Treatment GL [2024]
We recommend a laparoscopic approach as the first line in abdominal surgery for CD [EL2]

A Cochrane review of two randomized trials[188,189] showed no difference in complications between laparoscopic and open surgery for CD. A more recent review[190] showed a benefit for patients operated by laparoscopy, with fewer complications and lower rate of incisional hernia. This review included both randomized trials and observational studies. While this may potentially introduce some bias, based on strong evidence for the benefits of laparoscopy, especially in relation to reduced adhesions, the current evidence strongly supports recommending laparoscopy as the first-line approach. Laparoscopic resection for recurrent CD is also feasible but is associated with higher risk for conversion.[191]

Accepted Manuscript

Downloaded from https://academic.oup.com/ecco-jcc/advance-article/doi/10.1093/ecco-jcc/jjae089/7693896 by KU Leuven Libraries user on 04 July 2024

Manuscript Doi: 10.1093/ecco-jcc/jjae089

Importantly, in the absence of expertise to perform laparoscopic surgery, emergency operations should not be delayed.

Statement 4.12 ECCO CD Treatment GL [2024]
We recommend laparoscopic resection as an alternative to infliximab [EL2] or adalimumab [EL4] therapy in patients with limited terminal ileal or ileocecal disease

A randomized, controlled, open-label, multicentre trial assigned 143 patients with non-stricturing CD of the terminal ileum to receive either laparoscopic ileocecal resection [*n* = 73] or infliximab [*n* = 70]. At 12-month follow-up, quality of life and body-image perception were comparable.[192] Patients treated with infliximab had fewer days of sick leave from work. Serious complications related to treatment occurred in 4 resected patients versus 2 in the anti-TNF group. Crossover among groups was needed in 37% of patients treated with infliximab and in 26% of those who underwent surgery. Long-term data from the randomized trial revealed no surgical recurrence in the surgery group after 5 years, while 50% in the anti-TNF group had surgery at 5 years.[193] A recent meta-analysis suggests reduced risk of overall and surgical recurrence and reduced use of postoperative biologic therapy if surgery is performed early.[194] Based on these data, early surgery has a benefit in patients with limited terminal ileal CD and represents a reasonable alternative to escalating medical therapy. Patients should be advised early about a surgical option.

Statement 4.13 ECCO CD Treatment GL [2024]
We suggest stapled side-to-side anastomoses in small-bowel or ileocolic resections for CD [EL3]

Surgeons place great importance on the technical aspects of their work, which can be influenced by various factors, including their training, personal experience, available resources, and the clinical scenario. The choice of the optimal anastomosis technique in small-bowel and ileocolic resections has been a subject of controversy. In recent years, there has been a growing body of evidence supporting the use of side-to-side anastomosis, and this support has been consistent over time.

A significant meta-analysis on 661 patients operated for cancer and CD revealed a significantly higher anastomotic leak rate in end-to-end anastomoses compared with side-to-side anastomoses [OR: 4.37; *p* = 0.02]. This was also observed in the subgroup of ileocolic

Accepted Manuscript

Downloaded from https://academic.oup.com/ecco-jcc/advance-article/doi/10.1093/ecco-jcc/jjae089/7693896 by KU Leuven Libraries user on 04 July 2024

anastomoses [OR: 3.8; $p = 0.05$].[195] Furthermore, overall postoperative complications [OR: 2.64; $p < 0.001$] and hospital stay length were higher [by 2.81 days; $p = 0.007$] when an end-to-end anastomosis was performed. A subsequent meta-analysis confirmed the superiority of side-to-side anastomosis in overall postoperative complications [OR 0.6; $p = 0.01$]. However, there were no statistically significant differences in leak rates, endoscopic and symptomatic recurrence, or reoperation for recurrence.[196]

A meta-analysis compared 396 stapled side-to-side anastomoses with 425 hand-sewn end-to-end anastomoses and found that stapled side-to-side anastomoses outperformed in all endpoints, namely overall postoperative complications [OR: 0.54; 95% CI: 0.32–0.93], anastomotic leak [OR: 0.45; 95% CI: 0.20–1.00], recurrence [OR: 0.20; 95% CI: 0.07–0.55], and reoperation for recurrence [OR: 0.18; 95% CI: 0.07–0.45].[197]

A network meta-analysis of 11 trials and 1113 patients further substantiated the superiority of stapled side-to-side anastomosis regarding overall complications, clinical recurrence, and reoperation for recurrence. However, the choice of anastomosis technique did not seem to affect leak rates, surgical-site infections, mortality, or length of hospital stay.[198] A more recent systematic review suggested that stapled side-to-side anastomoses may lower the risk of surgical recurrence in CD, potentially reducing rates of reoperations compared with hand-sewn end-to-end anastomoses [OR: 0.22; 95% CI: 0.05–0.95].[199] In case of emergency bowel resection, a retrospective study involving 92 bowel resections recommended use of stapled side-to-side anastomoses, which was associated with fewer endoscopic recurrences than hand-sewn end-to-end anastomoses [OR: 38.12; $p = 0.01$].[200] This was corroborated by another retrospective study.[201] However, a recent multicentre, retrospective, observational study examining 427 intestinal anastomoses in CD found no significant difference in postoperative complications.[202]

Overall, the quality of the studies included in systematic reviews and meta-analyses was notably limited, with only a minority of patients participating in RCTs and heterogenous populations studied. Despite this limitation, the prevailing consensus leans toward a preference for stapled side-to-side anastomosis, which is associated with lower rates of postoperative complications and allows for an intracorporeal anastomosis. Furthermore, it was suggested that the diameter of the anastomosis may be a significant risk factor for recurrence, as a wider anastomosis is thought to be associated with a reduced likelihood of clinical and surgical recurrences. Importantly, the width of the anastomosis is determined by its inlet, more than by the length of a staple line or a suture line. Endoscopic appraisal of an early recurrence should consider the type of anastomosis healing. Indeed, stapled [everted mucosa] and hand-sewn [inverted mucosa] have a different healing pattern and healing time,

Accepted Manuscript

Downloaded from https://academic.oup.com/ecco-jcc/advance-article/doi/10.1093/ecco-jcc/jjae089/7693896 by KU Leuven Libraries user on 04 July 2024

Manuscript Doi: 10.1093/ecco-jcc/jjae089

which should neither be confused endoscopically with an early recurrence, nor lead to overtreatment.

Statement 4.14 ECCO CD Treatment GL [2024]

We suggest that the Kono-S anastomosis can be an alternative surgical approach to other types of anastomoses after ileocecal resection [EL3]

Kono-S anastomosis was first described in 2011 as a new hand-sewn anti-mesenteric functional end-to-end anastomosis designed with the aim to reduce anastomotic CD recurrence after ileocecal resection.

In the first retrospective study,[203] Kono-S anastomosis was associated with a reduction in both median endoscopic recurrence score [Rutgeerts' score] and surgical recurrence rate at 5 years with no safety issues. These findings were then confirmed by a larger international multicentre retrospective study including 187 patients, reporting a 10-year surgical recurrence-free rate of 98.6%.[204]

Performing a Kono-S anastomosis was associated with longer operative time, similar short-term outcomes, and likely lower endoscopic recurrence rate than side-to-side anastomosis.[205] In another two retrospective cohort studies following patients for up to 5 years, Kono-S anastomosis was associated with a lower leak rate than end-to-end anastomosis[206] or stapled anastomosis[207], which in the authors' opinion could explain the lower surgical recurrence rate observed in the long term.

More recently, early results from the first RCT[208] comparing Kono-S and side-to-side anastomoses demonstrated a significant reduction in the 6-month endoscopic recurrence rate and mean Rutgeerts' score, comparable postoperative outcomes, and a trend toward a reduced surgical recurrence rate, although this was not statistically significant. This and other trials are still ongoing with definitive results expected in the near future.

Several meta-analyses, including the aforementioned RCT and observational studies, concluded that Kono-S anastomosis was associated with a reduced endoscopic recurrence rate and comparable short-term outcomes.[199,209,210] More limited evidence suggested a reduction in surgical recurrence and leak rate in Kono-S anastomosis than with conventional anastomoses. However, the most recent prospective study on Kono-S did not confirm a reduction in endoscopic recurrence rates and reported similar Rutgeerts' scores and clinical recurrence rates between conventional anastomosis and Kono-S.[211] Therefore, a definitive conclusion on the benefit of a Kono-S anastomosis cannot yet be made. Multicentre RCTs

Accepted Manuscript

Downloaded from https://academic.oup.com/ecco-jcc/advance-article/doi/10.1093/ecco-jcc/jjae089/7693896 by KU Leuven Libraries user on 04 July 2024

are currently ongoing across the US and Europe and will probably provide definitive answers on the role of Kono-S anastomosis.[212-214]

Statement 4.15 ECCO CD Treatment GL [2024]
There is insufficient evidence to recommend extensive mesenteric excision in surgery for ileocecal CD [EL4]

Extensive mesenteric excision may reduce the incidence of recurrence after resection by possibly removing a 'sump' of pro-inflammatory substances from the vicinity of the anastomosis. The current evidence for this is weak. Two systematic reviews addressed extensive mesenteric excision[199,209] but both only included one small historical case-control study.[215] This single case-control study compared 30 patients undergoing extensive mesenteric excision with a surgical recurrence rate of 2.9% at 5 years to a historical control group of 34 patients who had a 5-year recurrence rate of 40%.[215] Several ongoing trials address the possible benefit of a wide mesenteric excision in the context of CD. Such an excision cannot currently be recommended in routine care.

Statement 4.16 ECCO CD Treatment GL [2024]
We suggest a temporary stoma formation in patients with CD if they are not sufficiently optimized for surgery [EL4]

The decision to create a stoma [primary anastomosis and protective stoma or no anastomosis and split stoma] in the context of steroid intake relies mostly on clinical grounds and experience. There are limited data comparing strategies between primary anastomosis or secondary anastomosis in patients with CD treated with steroids.[216] However, prolonged [>6 weeks] and high-dose [≥20 mg prednisolone equivalent] steroid use are associated with postoperative infectious complications, including anastomotic leakage.[149,174,217,218]

Statement 4.17 ECCO CD Treatment GL [2024]
We recommend strictureplasty as an alternative treatment option to resection in small-bowel CD [EL2]

Accepted Manuscript

Downloaded from https://academic.oup.com/ecco-jcc/advance-article/doi/10.1093/ecco-jcc/jjae089/7693896 by KU Leuven Libraries user on 04 July 2024

Manuscript Doi: 10.1093/ecco-jcc/jjae089

Location of CD in the ileum, use of biologics before surgery, and non-conventional strictureplasty [SP] predict early site-specific recurrence after SP.[219,220] However, procedure-specific recurrence rates are available only for some SP techniques.[221] The wide range of recurrence rates after SP [3–25%] reflects the variability of the population case mix and most importantly of the follow-up length.[220] An extended follow-up time [>5 years] is mandatory to appraise the true outcome of SP.[220] Morbidity and postoperative hospital length of stay were similar for bowel resection and SP.[221-223] Overall, the results of SP compare well with the recurrence rate after bowel resection, while preserving bowel length.

Statement 4.18 ECCO CD Treatment GL [2024]
We suggest segmental colectomy in selected cases of colonic CD [EL4]

When a single colonic segment is affected, a segmental colectomy may be the recommended course of action. On the other hand, the involvement of multiple colon segments generally indicates [sub]total colectomy. A meta-analysis compared 223 cases of subtotal or total colectomies with ileorectal anastomosis and 265 cases of segmental colectomies in CD.[224] In this analysis, there were no significant differences in recurrence rates, complications, or need for a permanent stoma. However, it is worth noting that recurrence occurred on average 4.4 years later in patients who underwent a subtotal or total colectomy [$p < 0.001$].

A recent meta-analysis included patients who underwent segmental colectomy [$n = 500$], subtotal colectomy [$n = 510$], or total proctocolectomy [$n = 426$]. Complications were more frequent after segmental colectomy compared with subtotal colectomy [OR: 2.84; 95% CI: 1.16–6.96] and after proctocolectomy compared with subtotal colectomy [OR: 0.19; 95% CI: 0.09–0.38].[225] This indicates that subtotal colectomy is generally considered a safer procedure, although segmental colectomy resulted in fewer patients requiring permanent stoma [OR: 0.52; 95% CI: 0.35–0.77]. Subtotal colectomy had higher rates of CD recurrence [OR: 3.53; 95% CI: 2.45–5.10] and need for repeat surgery [OR: 3.52; 95% CI: 2.27–5.44] than total proctocolectomy. However, no significant difference in recurrence was observed between segmental and subtotal colectomy. In rare situations where two distinct colon segments are affected, it may be worth considering two segmental resections as an alternative to subtotal colectomy, particularly for patients who have extensive small-bowel loss. [11]

A recent retrospective analysis that included 55 [sub]total colectomies and 30 segmental colonic resections indicated a trend towards increased postoperative complications after

Accepted Manuscript

Downloaded from https://academic.oup.com/ecco-jcc/advance-article/doi/10.1093/ecco-jcc/jjae089/7693896 by KU Leuven Libraries user on 04 July 2024

Manuscript Doi: 10.1093/ecco-jcc/jjae089

segmental colectomy [Clavien-Dindo grade ≥ III] of 13.3% versus 7.3% after [sub]total colectomy. Additionally, there was a trend toward higher rates of hospital readmissions [13.3% vs 1.8%] and reinterventions [13.3% vs 3.6%] after segmental resection compared with [sub]total colectomy.[226] Another recent multicentre retrospective study including 687 patients concluded that segmental resection was a safe option compared with total colectomy with the additional benefit of reducing ostomy formation without increasing the risk of surgical recurrence, particularly in the era of biologics.[227] However, the heterogeneity of the included patients was a limitation of this analysis.

A further retrospective, single-centre study included 200 patients who underwent segmental colectomy. A surgical recurrence rate of 31% was observed. Risk factors of recurrence and subsequent [sub]total colectomy in multivariate analysis were the presence of three or more affected sites [HR: 2.47; 95% CI: 1.22–5.00; p = 0.018] and presence of perianal disease [HR: 3.23; 95% CI: 1.29–8.07; p = 0.006].[228]

In summary, the extent of colonic resection is determined by the clinical presentation [elective vs emergency surgery] and by the number of colonic segments involved [unisegmental vs pancolitis]. Segmental colectomy is generally favoured whenever feasible as this does not increase the risk of recurrence, particularly in the modern era of biologics and when other risk factors for recurrence [such as number of affected locations and presence of perianal disease] are absent.

Statement 4.19 ECCO CD Treatment GL [2024]

We suggest proctocolectomy as a treatment for CD-associated colorectal cancer or high-grade dysplasia and segmental colectomy followed by endoscopic surveillance in selected cases [EL3]

Patients with chronic inflammation of the large bowel are at an increased risk of development of colorectal cancer [CRC], as described in an European Evidence-based Consensus: IBD and Malignancies.[229] Two meta-analyses of cohort studies have clarified the increased risk of CRC in patients with IBD.[230,231] The pooled standardized incidence ratio [SIR] for CRC was 1.7 [95% CI: 1.2–2.2] in all patients with IBD and 1.9 in CD [95% CI: 1.4–2.5]. However, the HR of CRC increased in all age groups [HR: 1.40; 95% CI: 1.27–1.53], consistent with a recent Scandinavian cohort study.[231] There was higher risk with extensive colitis and younger IBD diagnosis [age <30 years], with a SIR of 6.4 [95% CI: 2.4–17.5] and

Accepted Manuscript

Downloaded from https://academic.oup.com/ecco-jcc/advance-article/doi/10.1093/ecco-jcc/jjae089/7693896 by KU Leuven Libraries user on 04 July 2024

Manuscript Doi: 10.1093/ecco-jcc/jjae089

7.2 [95% CI: 2.9–17.8], respectively. Cumulative risks of cancer were 1%, 2%, and 5% after 10, 20, and >20 years disease duration, respectively.

These reports indicate that the risk of CRC is increased in patients with IBD, but not to the extent previously reported and not in all patients.

In a Danish cohort,[232] CRC patients with CD had a lower frequency of Duke's A- and B-stage tumours [36% vs 42%] and a higher frequency of Duke's C- [31% vs 27%] and D-stage tumours [23% vs 21%], whereas the frequency of unknown-stage tumours [10%] resembled that of non IBD-related CRC. The 5-year adjusted mortality rate ratios for patients with ulcerative colitis [UC] or CD were increased by 1.14 [95% CI: 1.03–1.27] and 1.26 [95% CI: 1.07–1.49], respectively, compared with patients without IBD. In contrast, in an Irish population-based study, patients with IBD-related CRC were about 7 years younger at cancer diagnosis than patients with non-IBD CRC but survived about 3 years longer. Older age, male sex, smoking, and advanced CRC grade and stage were independently associated with shorter survival times. When propensity score matching was used to analyse outcomes, the survival times of CRC patients with and without IBD were not significantly different.[233] Taken together, these results reveal that patients with IBD tend to develop CRC at younger ages than patients without IBD. However, no effect of IBD on patient survival has been consistently demonstrated.

The risk of CRC in CD increases with longer disease duration, extent of colitis, a familial history of CRC, coexistent primary sclerosing cholangitis, and the degree and duration of inflammation. CRC in CD tends to have higher histological grade and more often mucinous/signet-ring histological characteristics.[11,229,234-236]

The previous ECCO-ESCP Consensus on Surgery for CD[11] recommended proctocolectomy in fit patients with preoperative diagnosis of cancer or high-grade dysplasia due to the multifocal nature of dysplasia in CD colitis and the reported high rate of metachronous colon cancer after segmental surgical resection.[237,238] However, caution is required when comparing cancer incidence between patients with CD undergoing regular colonoscopies and the general population offered cancer screening; lead time bias may overestimate a possible causal association. Furthermore, the onset of CD is often unclear, while many cancers are diagnosed concomitantly or immediately after a diagnosis of CD and thus have a debatable association with CD. Indeed, the incidence of metachronous CRC after segmental resection is much lower than initially thought[239-241] and the prior reported high rate of metachronous cancer may be attributed to inadequate surgery or even underestimation of synchronous tumours. Furthermore, most of the available data originate from the early 1970s, when both endoscopic and therapeutic interventions were very different from current standards.

Downloaded from https://academic.oup.com/ecco-jcc/advance-article/doi/10.1093/ecco-jcc/jjae089/7693896 by KU Leuven Libraries user on 04 July 2024

Manuscript Doi: 10.1093/ecco-jcc/jjae089

Therefore, segmental resections and endoscopic surveillance may be proposed in selected patients after proper consent or in patients who are at high risk for surgery.

Importantly, patients with CRC in CD should be operated according to the principles of oncological surgery, including adequate lymphadenectomy.[242,243] The same principles of oncological surgery should be considered in the presence of a colonic stenosis and long-lasting extensive CD colitis can easily be missed upon endoscopic biopsy. Strictureplasty is not recommended in this context.[11,237]

Statement 4.20 ECCO CD Treatment GL [2024]

We suggest a defunctioning stoma for non-acute refractory CD colitis to delay or avoid the need for colectomy [EL5]

The following two options may be discussed in the presence of refractory CD colitis: a [sub]total colectomy, particularly as a potentially life-saving procedure in fulminant colitis, and a defunctioning ileostomy to divert the faecal stream and allow for remission, together with intensified medical therapy [244]. A diverting ileostomy may delay further procedures, facilitate perioperative optimization, and allow for a limited resection if required at a later stage [i.e. segmental colectomy]. The clinical scenario in which a diverting stoma is performed to aid the management of extensive perineal disease is covered elsewhere and is not the focus of the present statement.

The literature preceding the biologic era reported initial remission rates of up to 90%[245-248] following creation of a defunctioning stoma, which is more than the 50–80% reported in more recent series.[249,250] Lasting restoration of bowel continuity/stoma reversal was effective in up to two-thirds of patients but was much lower when perianal disease was also present [i.e. 29–42%.][6,7] Surgical complications of defunctioning stoma creation were in the expected range of 3–10% for stoma prolapse/hernia and <5% for renal failure due to high-output stoma.[250] Further bowel resection was reported in up to half of the patients in recent series.[249,250] Risk factors for proctocolectomy were severe refractory perianal disease, requirement for combined medical therapy, and a history of more than one biologic drug. For these patients, early colectomy and end ileostomy [as opposed to a defunctioning ileostomy] may be discussed.

The following factors should be taken into account when a proctocolectomy is required and ileal pouch anal anastomosis is considered. In general, more patients have postoperative pelvic sepsis and a higher pouch failure rate when compared with patients with IPAA for UC. Patients also have more bowel movements and daytime incontinence when compared with

Accepted Manuscript

Downloaded from https://academic.oup.com/ecco-jcc/advance-article/doi/10.1093/ecco-jcc/jjae089/7693896 by KU Leuven Libraries user on 04 July 2024

Manuscript Doi: 10.1093/ecco-jcc/jjae089

patients with IPAA for UC. It is worth noting that in selected patients with isolated CD colitis without small-bowel or perianal involvement, outcomes similar to patients with IPAA for UC can be obtained [no difference in pelvic sepsis, stool frequency, incontinence, score on quality-of-life surveys, or pouch failure].[251-256]

Statement 4.21 ECCO CD Treatment GL [2024]

We recommend CD surgery is performed in high-volume IBD centres [EL3]

The data and appreciation of the benefit of centralization of IBD surgery in high-volume centres is controversial. Nationwide studies suggested lower mortality in high-volume centres, although patients who are frailer and sicker are over-represented in these centres.[257,258] The definition of a high-volume, expert centre and of referral criteria are particularly controversial. ECCO has defined quality-of-care criteria and standards for the care of IBD patients, including patient volume, in a position paper.[259]

Practice points

When surgery becomes necessary, it is important to thoroughly assess the bowel, ideally preoperatively with MRI enterography. MRI enterography may reveal a distinction between inflammatory strictures [amenable to intensified medical therapy] and fibrotic strictures. Systematically assessing the bowel during surgery may identify further strictures. To maximize bowel preservation, the IBD surgeon should be familiar with the different kinds of strictureplasties, including non-conventional strictureplasties. Nonetheless, strictureplasty of the colon is not recommended.[260]

The anastomotic technique of choice is not firmly established, although a stapled side-to-side anastomosis is suggested in small-bowel or ileocolic resections. While segmental colectomy is advisable when a single colon segment is involved, an oncologic proctocolectomy is recommended when colonic dysplasia or a neoplasia is identified.

Accepted Manuscript

Downloaded from https://academic.oup.com/ecco-jcc/advance-article/doi/10.1093/ecco-jcc/jjae089/7693896 by KU Leuven Libraries user on 04 July 2024

Manuscript Doi: 10.1093/ecco-jcc/jjae089

4.2 Postoperative management

Statement 4.22 ECCO CD Treatment GL [2024]
We recommend endoscopic surveillance within 6–12 months after surgical resection in CD [EL2]

A systematic review that included one unblinded RCT and four retrospective cohort studies revealed a lower recurrence rate in the endoscopy-based management group than in the control group.[261] Similarly, another systematic review concluded that mucosal changes can be observed in up to 73% of cases within 1 year after surgical resection when patients undergo endoscopic monitoring.[262]

In a study that randomized 174 patients in a 2:1 ratio, some underwent colonoscopy at 6 months with active therapy while others did not undergo colonoscopy and received standard care. At the 18-month timepoint, clinical recurrence was lower [37.7% vs 46.1%; RR 0.82; 95% CI: 0.56–1.18] in the colonoscopy group and endoscopic recurrence was higher in the group that received standard care compared with those under active surveillance [67% vs 49%; $p = 0.03$].[263]

Another systematic review that included 26 prospective studies reported the presence of mucosal lesions in up to 70% of cases with a median endoscopic follow-up of 12 months. Notably, more than 50% of these lesions were located at the anastomotic site. Interestingly, despite receiving medical treatment, 41% of patients exhibited significant lesions.[264] These findings are consistent with similar results presented by other studies.[265,266] Endoscopic monitoring within 6–12 months following surgical resection allows for identification of patients who may experience disease recurrence, even with ongoing medical therapy, enabling proactive intervention.

Statement 4.23 ECCO CD Treatment GL [2024]
We suggest postoperative prophylactic medical therapy after ileocolic resection in patients with CD at high risk of recurrence [EL3]

Prophylaxis for postoperative recurrence is recommended in patients at high risk for recurrence. Thiopurines appear to be more effective than placebo in preventing postoperative recurrence according to different studies.[267] Infliximab was more effective than placebo in preventing endoscopic, but not clinical, recurrence in the prospective PREVENT

Accepted Manuscript

Downloaded from https://academic.oup.com/ecco-jcc/advance-article/doi/10.1093/ecco-jcc/jjae089/7693896 by KU Leuven Libraries user on 04 July 2024

Manuscript Doi: 10.1093/ecco-jcc/jjae089

trial.[268] Overall, anti-TNF agents are the most effective therapy in preventing postoperative endoscopic recurrence.[269] More recent evidence from observational studies described the efficacy of biologics with different mechanisms of action [ustekinumab and VDZ] in prevention of recurrence.[270] A prospective study presented in abstract form demonstrated that VDZ was more efficacious than placebo in preventing endoscopic recurrence. Patients treated with VDZ had a 77.8% chance of having a lower Rutgeerts' score than patients with placebo 6 months after an ileocolic resection [$p < 0.0001$].[271] A retrospective multicentre study from Spain analysed postoperative recurrence rates in 40 patients treated with ustekinumab and 25 treated with VDZ [all had previous exposure to anti-TNF]. The cumulative probability of clinical postoperative recurrence at 12 months after surgery was 32% and 30% for ustekinumab and VDZ, respectively. The rate of endoscopic recurrence was 42% for ustekinumab and 40% for VDZ.[272] High-risk patients include those that smoke, have penetrating disease, or present with an IASC, fistula, or both.[273,274]

Statement 4.24 ECCO CD Treatment GL [2024]

We recommend extended thromboembolism prophylaxis following hospital discharge after CD surgery [EL2]

Although thromboprophylaxis is well documented in patients who have surgery after CRC, there is limited evidence in IBD. A recent systematic review suggested that postoperative DVT risk was similar in IBD to that of patients with advanced CRC. The risk was highest in those who had a subtotal colectomy or a proctectomy. The dosage of low molecular weight heparin was also assessed in a single-centre study, suggesting that a dose of 4000 IU/day of low molecular weight heparin was insufficient for IBD patients.[275] A minimal duration of thromboprophylaxis of 2 weeks postoperatively was suggested.[276]

5. Conclusion

There are many options and crossroads in decision making for surgery in CD. Some approaches have been tested over time and were described in these surgical guidelines. Although sufficient training, technical expertise, and an adequate caseload to achieve and maintain subspecialization in IBD surgery are important, the key to success in managing CD is a multidisciplinary team, as no specialist alone can solve the CD equation. The present

Downloaded from https://academic.oup.com/ecco-jcc/advance-article/doi/10.1093/ecco-jcc/jjae089/7693896 by KU Leuven Libraries user on 04 July 2024

Manuscript Doi: 10.1093/ecco-jcc/jjae089

guidelines have been written with this interdisciplinary approach in mind and summarize the currently available knowledge. The degree of certainty in some aspects of surgery for CD is closer to eminence than evidence, thus paving the way for further research and better answers. Consideration of patient lifestyle preference is integral to shared decision making and key to achieve best standard of care. Revealing gaps in evidence is the first step, as research focused on clinical needs and gaps in the current evidence will inform guideline updates. Meanwhile, dynamic integration of gains in knowledge into the ECCO e-Guide will allow for rapid dissemination. Guidelines provide guidance to the clinician, who adapt expert knowledge, generic evidence and patient lifestyle preference to individualize care. It is hoped that the present work will contribute to optimizing care for patients with CD.

Accepted Manuscript

Downloaded from https://academic.oup.com/ecco-jcc/advance-article/doi/10.1093/ecco-jcc/jjae089/7693896 by KU Leuven Libraries user on 04 July 2024

Manuscript Doi: 10.1093/ecco-jcc/jjae089

Funding

This project was initiated, funded, and supported by the ECCO.

Acknowledgements

We gratefully thank Dr Paul Freudenberger for the literature search and full-text retrieval; Torsten Karge for support on informatics and on the web Guidelines platform; and the ECCO Office for logistical and coordination support.

We gratefully thank the EFCCA patient representatives Bastien Corsat, Xavier Donnet, Evelyn Gross, Antonio Valdivia, Janek Kapper, and Lucie Lastikova who proactively collaborated in the development of these Guidelines.

We thank Ibrahim Ethem Gecim for his work in the abstract screening process.

We would like to thank and acknowledge the ECCO National Representatives and additional reviewers, who acted as external reviewers and provided suggestions on the recommendations and supporting text to this document: Pascal Juillerat, Allesandra Soriano, Mark Samaan, Tiago Cúrdia Gonçalves, Edoardo Savarino, Federica Furfaro, Davide Giuseppe Ribaldone, Gulustan Babayeva-Sadiqova, Aurelien Amiot, Gianmichele Meucci, Iago Rodríguez Lago, Mathieu Uzzan, Gerassimos Mantzaris, Beatriz Gros Alcalde, Vito Annese, Eduard Brunet Mas, Maria Jose Garcia, Eirini Zach, John Marshall, Carla Felice, Maha Maher, Paul Pollack, Andreas Blesl, Negreanu Lucian, Ferdinando D'Amico, Dimitrios Karagiannis, Patrick Allen, Oliver Bachmann, Imerio Angriman, Anna Kagramanova, Dahham Alsoud, Natália Queiroz, Usha Chauhan, Petra Golovics, Chen Sarbagili, Lorenzo Bertani, Ulf Helwig, Clas-Göran af Björkesten, Ante Bogut, Anthony Buisson, Ignacio Catalan-Serra, Aslı Çifcibaşı Örmeci, Marco Daperno, Mihai Mircea Diculescu, Dana Duricová, Piotr Eder, Magdalena Gawron-Kiszka, Ayal Hirsch, Ondrej Hradsky, Hendrik Laja, Sara Onali, Samuel Raimundo Fernandes, Christian Philipp Selinger, Helena Tavares de Sousa, Svetlana Turcan, Sophie Vieujean, and Yamile Zabana.

Accepted Manuscript

Downloaded from https://academic.oup.com/ecco-jcc/advance-article/doi/10.1093/ecco-jcc/jjae089/7693896 by KU Leuven Libraries user on 04 July 2024

Manuscript Doi: 10.1093/ecco-jcc/jjae089

Authors' contribution

Michel Adamina, Pär Myrelid, Hannah Gordon, and Tim Raine coordinated the project; Silvia Minozzi provided expert methodology advice, trained the working group members, and performed the analysis of data; Uri Kopylov, Bram Verstockt, Maria Chaparro, Christianne Buskens, and Janindra Warusavitarne coordinated the working groups; all the Authors listed contributed to the identification of relevant data, data interpretation, and drafted and discussed the final recommendations; all Authors participated in the final Consensus; Michel Adamina and Pär Myrelid drafted this manuscript.

Conflict of interests

ECCO has diligently maintained a disclosure policy of potential conflicts of interest [CoI]. The conflict-of-interest declaration is based on a form used by the International Committee of Medical Journal Editors [ICMJE]. The CoI statement is not only stored at the ECCO Office and the editorial office of JCC but is also open to public scrutiny on the ECCO website [https://www.ecco-ibd.eu/about-ecco/ecco-disclosures.html], providing a comprehensive overview of potential conflicts of interest of authors.

Disclaimer

The ECCO Guidelines are targeted at health care professionals only and are based on an international consensus process.

This process includes intensive literature research as explained in the methodology section and may not reflect subsequent scientific developments, if any, until the next Guidelines update is prepared. Readers of the Guidelines acknowledge that research about medical and health issues is constantly evolving and diagnoses, treatments, and dose schedules for medications are being revised continually. Therefore, the European Crohn´s and Colitis Organisation (ECCO) encourages all readers to also consult the most up-to-date published product information and data sheets provided by the manufacturers as well as the most recent codes of conduct and safety regulations.

Any treatment decisions are to be made at the sole discretion and within the exclusive responsibility of the individual clinician and should not be based exclusively on the content of

Accepted Manuscript

Downloaded from https://academic.oup.com/ecco-jcc/advance-article/doi/10.1093/ecco-jcc/jjae089/7693896 by KU Leuven Libraries user on 04 July 2024

Manuscript Doi: 10.1093/ecco-jcc/jjae089

the ECCO Guidelines. The European Crohn´s and Colitis Organisation (ECCO) and/or any of its staff members and/or any consensus contributor may not be held liable for any information published in good faith in the ECCO Consensus Guidelines. ECCO makes no representations or warranties, express or implied, as to the accuracy or completeness of the whole or any part of the Guidelines. ECCO does not accept, and expressly disclaims, responsibility for any liability, loss or risk that may be claimed or incurred as a consequence of the use or application of the whole or any part of the Guidelines.

When the Guidelines mention trade names, commercial products or organizations, this does not constitute any endorsement by ECCO and/or any consensus contributor.

Accepted Manuscript

Downloaded from https://academic.oup.com/ecco-jcc/advance-article/doi/10.1093/ecco-jcc/jjae089/7693896 by KU Leuven Libraries user on 04 July 2024

Manuscript Doi: 10.1093/ecco-jcc/jjae089

References

1. Ng SC, Shi HY, Hamidi N*, et al.* Worldwide incidence and prevalence of inflammatory bowel disease in the 21st century: A systematic review of population-based studies. *Lancet* 2018;**390**:2769-78.
2. Frolkis AD, Dykeman J, Negron ME*, et al.* Risk of surgery for inflammatory bowel diseases has decreased over time: A systematic review and meta-analysis of population-based studies. *Gastroenterology* 2013;**145**:996-1006.
3. Adamina M, Gerasimidis K, Sigall-Boneh R*, et al.* Perioperative dietary therapy in inflammatory bowel disease. *J Crohns Colitis* 2019.
4. Bouguen G, Peyrin-Biroulet L. Surgery for adult crohn's disease: What is the actual risk? *Gut* 2011;**60**:1178-81.
5. Burke JP, Velupillai Y, O'Connell PR, Coffey JC. National trends in intestinal resection for crohn's disease in the post-biologic era. *Int J Colorectal Dis* 2013;**28**:1401-6.
6. Bemelman WA, collaborators SE. Evolving role of ibd surgery. *J Crohns Colitis* 2018;**12**:1005-7.
7. Lightner AL, Shen B. Perioperative use of immunosuppressive medications in patients with crohn's disease in the new "biological era". *Gastroenterol Rep (Oxf)* 2017;**5**:165-77.
8. Reinglas J, Gonczi L, Kurt Z, Bessissow T, Lakatos PL. Positioning of old and new biologicals and small molecules in the treatment of inflammatory bowel diseases. *World J Gastroenterol* 2018;**24**:3567-82.
9. Reinglas J, Restellini S, Gonczi L*, et al.* Harmonization of quality of care in an ibd center impacts disease outcomes: Importance of structure, process indicators and rapid access clinic. *Dig Liver Dis* 2019;**51**:340-5.
10. Koltun WA. Better together: Improved care of the ibd patient using the multi-disciplinary ibd center. *Expert Rev Gastroenterol Hepatol* 2017;**11**:491-3.
11. Bemelman WA, Warusavitarne J, Sampietro GM*, et al.* Ecco-escp consensus on surgery for crohn's disease. *J Crohns Colitis* 2018;**12**:1-16.
12. Harbord M, Annese V, Vavricka SR*, et al.* The first european evidence-based consensus on extra-intestinal manifestations in inflammatory bowel disease. *J Crohns Colitis* 2016;**10**:239-54.
13. Kemp K, Dibley L, Chauhan U*, et al.* Second n-ecco consensus statements on the european nursing roles in caring for patients with crohn's disease or ulcerative colitis. *J Crohns Colitis* 2018;**12**:760-76.
14. Maaser C, Sturm A, Vavricka SR*, et al.* Ecco-esgar guideline for diagnostic assessment in ibd part 1: Initial diagnosis, monitoring of known ibd, detection of complications. *J Crohns Colitis* 2019;**13**:144-64.
15. Sturm A, Maaser C, Calabrese E*, et al.* Ecco-esgar guideline for diagnostic assessment in ibd part 2: Ibd scores and general principles and technical aspects. *J Crohns Colitis* 2019;**13**:273-84.
16. Sturm A, Maaser C, Mendall M*, et al.* European crohn's and colitis organisation topical review on ibd in the elderly. *J Crohns Colitis* 2017;**11**:263-73.
17. Gordon H. Ecco guidelines on therapeutics in crohn's disease: Medical treatment. *J Crohns Colitis* 2024.

Accepted Manuscript

Downloaded from https://academic.oup.com/ecco-jcc/advance-article/doi/10.1093/ecco-jcc/jjae089/7693896 by KU Leuven Libraries user on 04 July 2024

18. Adamina M, Bonovas S, Raine T*, et al.* Ecco guidelines on therapeutics in crohn's disease: Surgical treatment. *J Crohns Colitis* 2020;**14**:155-68.
19. Torres J, Bonovas S, Doherty G*, et al.* Ecco guidelines on therapeutics in crohn's disease: Medical treatment. *J Crohns Colitis* 2020;**14**:4-22.
20. J. H, I. C, P. G*, et al.* Explanation of the 2011 oxford centre for evidence-based medicine (ocebm) levels of evidence (background document). https://www.cebm.net/index.aspx?o=5653 Accessed 09.11.2019, 2011.
21. Panes J, Rimola J. Perianal fistulizing crohn's disease: Pathogenesis, diagnosis and therapy. *Nat Rev Gastroenterol Hepatol* 2017;**14**:652-64.
22. Thia KT, Mahadevan U, Feagan BG*, et al.* Ciprofloxacin or metronidazole for the treatment of perianal fistulas in patients with crohn's disease: A randomized, double-blind, placebo-controlled pilot study. *Inflamm Bowel Dis* 2009;**15**:17-24.
23. Khan KJ, Ullman TA, Ford AC*, et al.* Antibiotic therapy in inflammatory bowel disease: A systematic review and meta-analysis. *Am J Gastroenterol* 2011;**106**:661-73.
24. Dewint P, Hansen BE, Verhey E*, et al.* Adalimumab combined with ciprofloxacin is superior to adalimumab monotherapy in perianal fistula closure in crohn's disease: A randomised, double-blind, placebo controlled trial (adafi). *Gut* 2014;**63**:292-9.
25. Klein M, Binder HJ, Mitchell M, Aaronson R, Spiro H. Treatment of crohn's disease with azathioprine: A controlled evaluation. *Gastroenterology* 1974;**66**:916-22.
26. Rhodes J, Bainton D, Beck P, Campbell H. Controlled trial of azathioprine in crohn's disease. *Lancet* 1971;**2**:1273-6.
27. Willoughby JM, Beckett J, Kumar PJ, Dawson AM. Controlled trial of azathioprine in crohn's disease. *Lancet* 1971;**2**:944-7.
28. Willoughby JM, Kumar P, Beckett J, Dawson AM. A double-blind trial of azathioprine in crohn's disease. *Gut* 1971;**12**:864.
29. Chande N, Patton PH, Tsoulis DJ, Thomas BS, MacDonald JK. Azathioprine or 6-mercaptopurine for maintenance of remission in crohn's disease. *Cochrane Database Syst Rev* 2015;**2015**:CD000067.
30. Present DH, Korelitz BI, Wisch N*, et al.* Treatment of crohn's disease with 6-mercaptopurine. A long-term, randomized, double-blind study. *N Engl J Med* 1980;**302**:981-7.
31. Present DH, Rutgeerts P, Targan S*, et al.* Infliximab for the treatment of fistulas in patients with crohn's disease. *N Engl J Med* 1999;**340**:1398-405.
32. Sands BE, Anderson FH, Bernstein CN*, et al.* Infliximab maintenance therapy for fistulizing crohn's disease. *N Engl J Med* 2004;**350**:876-85.
33. Gordon M, Sinopoulou V, Akobeng AK*, et al.* Infliximab for medical induction of remission in crohn's disease. *Cochrane Database Syst Rev* 2023;**11**:CD012623.
34. Davidov Y, Ungar B, Bar-Yoseph H*, et al.* Association of induction infliximab levels with clinical response in perianal crohn's disease. *J Crohns Colitis* 2017;**11**:549-55.
35. De Gregorio M, Lee T, Krishnaprasad K*, et al.* Higher anti-tumor necrosis factor-alpha levels correlate with improved radiologic outcomes in crohn's perianal fistulas. *Clin Gastroenterol Hepatol* 2022;**20**:1306-14.
36. Papamichael K, Vande Casteele N, Jeyarajah J*, et al.* Higher postinduction infliximab concentrations are associated with improved clinical outcomes in fistulizing crohn's disease: An accent-ii post hoc analysis. *Am J Gastroenterol* 2021;**116**:1007-14.

Accepted Manuscript

Downloaded from https://academic.oup.com/ecco-jcc/advance-article/doi/10.1093/ecco-jcc/jjae089/7693896 by KU Leuven Libraries user on 04 July 2024

37. Strik AS, Lowenberg M, Buskens CJ*, et al.* Higher anti-tnf serum levels are associated with perianal fistula closure in crohn's disease patients. *Scand J Gastroenterol* 2019;**54**:453-8.
38. Yarur AJ, Kanagala V, Stein DJ*, et al.* Higher infliximab trough levels are associated with perianal fistula healing in patients with crohn's disease. *Aliment Pharmacol Ther* 2017;**45**:933-40.
39. Colombel JF, Schwartz DA, Sandborn WJ*, et al.* Adalimumab for the treatment of fistulas in patients with crohn's disease. *Gut* 2009;**58**:940-8.
40. Colombel JF, Sandborn WJ, Rutgeerts P*, et al.* Adalimumab for maintenance of clinical response and remission in patients with crohn's disease: The charm trial. *Gastroenterology* 2007;**132**:52-65.
41. Echarri A, Castro J, Barreiro M*, et al.* Evaluation of adalimumab therapy in multidisciplinary strategy for perianal crohn's disease patients with infliximab failure. *J Crohns Colitis* 2010;**4**:654-60.
42. Lichtiger S, Binion DG, Wolf DC*, et al.* The choice trial: Adalimumab demonstrates safety, fistula healing, improved quality of life and increased work productivity in patients with crohn's disease who failed prior infliximab therapy. *Aliment Pharmacol Ther* 2010;**32**:1228-39.
43. Panaccione R, Colombel JF, Sandborn WJ*, et al.* Adalimumab maintains remission of crohn's disease after up to 4 years of treatment: Data from charm and adhere. *Aliment Pharmacol Ther* 2013;**38**:1236-47.
44. Castano-Milla C, Chaparro M, Saro C*, et al.* Effectiveness of adalimumab in perianal fistulas in crohn's disease patients naive to anti-tnf therapy. *J Clin Gastroenterol* 2015;**49**:34-40.
45. Plevris N, Jenkinson PW, Arnott ID, Jones GR, Lees CW. Higher anti-tumor necrosis factor levels are associated with perianal fistula healing and fistula closure in crohn's disease. *Eur J Gastroenterol Hepatol* 2020;**32**:32-7.
46. Sandborn WJ, Feagan BG, Stoinov S*, et al.* Certolizumab pegol for the treatment of crohn's disease. *N Engl J Med* 2007;**357**:228-38.
47. Schreiber S, Lawrance IC, Thomsen OO*, et al.* Randomised clinical trial: Certolizumab pegol for fistulas in crohn's disease - subgroup results from a placebo-controlled study. *Aliment Pharmacol Ther* 2011;**33**:185-93.
48. Feagan BG, Schwartz D, Danese S*, et al.* Efficacy of vedolizumab in fistulising crohn's disease: Exploratory analyses of data from gemini 2. *J Crohns Colitis* 2018;**12**:621-6.
49. Lee MJ, Parker CE, Taylor SR*, et al.* Efficacy of medical therapies for fistulizing crohn's disease: Systematic review and meta-analysis. *Clin Gastroenterol Hepatol* 2018;**16**:1879-92.
50. Schwartz DA, Peyrin-Biroulet L, Lasch K, Adsul S, Danese S. Efficacy and safety of 2 vedolizumab intravenous regimens for perianal fistulizing crohn's disease: Enterprise study. *Clin Gastroenterol Hepatol* 2022;**20**:1059-67 e9.
51. Sands B, Gasink C, Jacobstein D*, et al.* Fistula healing in pivotal studies of ustekinumab in crohn's disease. *Gastroenterology* 2017;**152**:S185.
52. Godoy Brewer GM, Salem G, Afzal MA*, et al.* Ustekinumab is effective for perianal fistulising crohn's disease: A real-world experience and systematic review with meta-analysis. *BMJ Open Gastroenterol* 2021;**8**.

Accepted Manuscript

Downloaded from https://academic.oup.com/ecco-jcc/advance-article/doi/10.1093/ecco-jcc/jjae089/7693896 by KU Leuven Libraries user on 04 July 2024

53. Colombel JF, Irving P, Rieder F*, et al.* Efficacy and safety of upadacitinib for the treatment of fistulas and fissures in patients with crohn's disease. *Journal of Crohn's and Colitis* 2023;**17**.
54. Davies M, Harris D, Lohana P*, et al.* The surgical management of fistula-in-ano in a specialist colorectal unit. *Int J Colorectal Dis* 2008;**23**:833-8.
55. Herissay A, Siproudhis L, Le Balc'h E*, et al.* Combined strategies following surgical drainage for perianal fistulizing crohn's disease: Failure rates and prognostic factors. *Colorectal Dis* 2021;**23**:159-68.
56. Morrison JG, Gathright JB, Jr., Ray JE*, et al.* Surgical management of anorectal fistulas in crohn's disease. *Dis Colon Rectum* 1989;**32**:492-6.
57. Papaconstantinou I, Kontis E, Koutoulidis V, Mantzaris G, Vassiliou I. Surgical management of fistula-in-ano among patients with crohn's disease: Analysis of outcomes after fistulotomy or seton placement-single-center experience. *Scandinavian journal of surgery : SJS : official organ for the Finnish Surgical Society and the Scandinavian Surgical Society* 2017;**106**:211-5.
58. Park MY, Yoon YS, Kim HE*, et al.* Surgical options for perianal fistula in patients with crohn's disease: A comparison of seton placement, fistulotomy, and stem cell therapy. *Asian J Surg* 2021;**44**:1383-8.
59. van der Hagen SJ, Baeten CG, Soeters PB, van Gemert WG. Long-term outcome following mucosal advancement flap for high perianal fistulas and fistulotomy for low perianal fistulas: Recurrent perianal fistulas: Failure of treatment or recurrent patient disease? *Int J Colorectal Dis* 2006;**21**:784-90.
60. Williams JG, Rothenberger DA, Nemer FD, Goldberg SM. Fistula-in-ano in crohn's disease. Results of aggressive surgical treatment. *Dis Colon Rectum* 1991;**34**:378-84.
61. Takesue Y, Ohge H, Yokoyama T*, et al.* Long-term results of seton drainage on complex anal fistulae in patients with crohn's disease. *J Gastroenterol* 2002;**37**:912-5.
62. Merten J, Eichelmann AK, Mennigen R*, et al.* Minor sphincter sparing surgery for successful closure of perianal fistulas in patients with crohn's disease. *J Clin Med* 2021;**10**.
63. Rozalen V, Pares D, Sanchez E*, et al.* Advancement flap technique for anal fistula in patients with crohn's disease: A systematic review of the literature. *Cir Esp* 2017;**95**:558-65.
64. Stellingwerf ME, van Praag EM, Tozer PJ, Bemelman WA, Buskens CJ. Systematic review and meta-analysis of endorectal advancement flap and ligation of the intersphincteric fistula tract for cryptoglandular and crohn's high perianal fistulas. *BJS Open* 2019;**3**:231-41.
65. Bessi G, Siproudhis L, Merlini l'Heritier A*, et al.* Advancement flap procedure in crohn and non-crohn perineal fistulas: A simple surgical approach. *Colorectal Dis* 2019;**21**:66-72.
66. Roper MT, Trinidad SM, Ramamoorthy SL*, et al.* Endorectal advancement flaps for perianal fistulae in crohn's disease: Careful patient selection leads to optimal outcomes. *J Gastrointest Surg* 2019;**23**:2277-84.
67. Seifarth C, Lehmann KS, Holmer C, Pozios I. Healing of rectal advancement flaps for anal fistulas in patients with and without crohn's disease: A retrospective cohort analysis. *BMC Surg* 2021;**21**:283.

Accepted Manuscript

Downloaded from https://academic.oup.com/ecco-jcc/advance-article/doi/10.1093/ecco-jcc/jjae089/7693896 by KU Leuven Libraries user on 04 July 2024

68. van Praag EM, Stellingwerf ME, van der Bilt JDW*, et al.* Ligation of the intersphincteric fistula tract and endorectal advancement flap for high perianal fistulas in crohn's disease: A retrospective cohort study. *J Crohns Colitis* 2020;**14**:757-63.
69. Emile SH, Khan SM, Adejumo A, Koroye O. Ligation of intersphincteric fistula tract (lift) in treatment of anal fistula: An updated systematic review, meta-analysis, and meta-regression of the predictors of failure. *Surgery* 2020;**167**:484-92.
70. Meima-van Praag EM, van Rijn KL, Monraats MA, Buskens CJ, Stoker J. Magnetic resonance imaging after ligation of the intersphincteric fistula tract for high perianal fistulas in crohn's disease: A retrospective cohort study. *Colorectal Dis* 2021;**23**:169-77.
71. Wood T, Truong A, Mujukian A, Zaghiyan K, Fleshner P. Increasing experience with the lift procedure in crohn's disease patients with complex anal fistula. *Tech Coloproctol* 2022;**26**:205-12.
72. Grimaud JC, Munoz-Bongrand N, Siproudhis L*, et al.* Fibrin glue is effective healing perianal fistulas in patients with crohn's disease. *Gastroenterology* 2010;**138**:2275-81, 81 e1.
73. Vidon M, Munoz-Bongrand N, Lambert J*, et al.* Long-term efficacy of fibrin glue injection for perianal fistulas in patients with crohn's disease. *Colorectal Dis* 2021;**23**:894-900.
74. Senejoux A, Siproudhis L, Abramowitz L*, et al.* Fistula plug in fistulising ano-perineal crohn's disease: A randomised controlled trial. *J Crohns Colitis* 2016;**10**:141-8.
75. Nasseri Y, Cassella L, Berns M, Zaghiyan K, Cohen J. The anal fistula plug in crohn's disease patients with fistula-in-ano: A systematic review. *Colorectal Dis* 2016;**18**:351-6.
76. Adamina M, Ross T, Guenin MO*, et al.* Anal fistula plug: A prospective evaluation of success, continence and quality of life in the treatment of complex fistulae. *Colorectal Dis* 2014;**16**:547-54.
77. Garg P, Song J, Bhatia A, Kalia H, Menon GR. The efficacy of anal fistula plug in fistula-in-ano: A systematic review. *Colorectal Dis* 2010;**12**:965-70.
78. Chase TJG, Quddus A, Selvakumar D, Cunha P, Cuming T. Vaaft for complex anal fistula: A useful tool, however, cure is unlikely. *Tech Coloproctol* 2021;**25**:1115-21.
79. Schwandner O. Video-assisted anal fistula treatment (vaaft) combined with advancement flap repair in crohn's disease. *Tech Coloproctol* 2013;**17**:221-5.
80. Adegbola SO, Sahnan K, Tozer PJ*, et al.* Symptom amelioration in crohn's perianal fistulas using video-assisted anal fistula treatment (vaaft). *J Crohns Colitis* 2018;**12**:1067-72.
81. Mennigen R, Laukotter M, Senninger N, Rijcken E. The otsc((r)) proctology clip system for the closure of refractory anal fistulas. *Tech Coloproctol* 2015;**19**:241-6.
82. Prosst RL, Joos AK. Short-term outcomes of a novel endoscopic clipping device for closure of the internal opening in 100 anorectal fistulas. *Tech Coloproctol* 2016;**20**:753-8.
83. de Groof EJ, Sahami S, Lucas C*, et al.* Treatment of perianal fistula in crohn's disease: A systematic review and meta-analysis comparing seton drainage and anti-tumour necrosis factor treatment. *Colorectal Dis* 2016;**18**:667-75.

Accepted Manuscript

Downloaded from https://academic.oup.com/ecco-jcc/advance-article/doi/10.1093/ecco-jcc/jjae089/7693896 by KU Leuven Libraries user on 04 July 2024

84. Feroz SH, Ahmed A, Muralidharan A, Thirunavukarasu P. Comparison of the efficacy of the various treatment modalities in the management of perianal crohn's fistula: A review. *Cureus* 2020;**12**:e11882.
85. Wasmann KA, de Groof EJ, Stellingwerf ME*, et al.* Treatment of perianal fistulas in crohn's disease, seton versus anti-tnf versus surgical closure following anti-tnf [pisa]: A randomised controlled trial. *J Crohns Colitis* 2020;**14**:1049-56.
86. McNamara DA, Brophy S, Hyland JM. Perianal crohn's disease and infliximab therapy. *Surgeon* 2004;**2**:258-63.
87. Tandon P, Rhee GG, Schwartz D, McCurdy JD. Strategies to optimize anti-tumor necrosis factor therapy for perianal fistulizing crohn's disease: A systematic review. *Dig Dis Sci* 2019;**64**:3066-77.
88. Yassin NA, Askari A, Warusavitarne J*, et al.* Systematic review: The combined surgical and medical treatment of fistulising perianal crohn's disease. *Aliment Pharmacol Ther* 2014;**40**:741-9.
89. Bouguen G, Siproudhis L, Gizard E*, et al.* Long-term outcome of perianal fistulizing crohn's disease treated with infliximab. *Clin Gastroenterol Hepatol* 2013;**11**:975-81 e1-4.
90. Regueiro M, Mardini H. Treatment of perianal fistulizing crohn's disease with infliximab alone or as an adjunct to exam under anesthesia with seton placement. *Inflamm Bowel Dis* 2003;**9**:98-103.
91. Gaertner WB, Decanini A, Mellgren A*, et al.* Does infliximab infusion impact results of operative treatment for crohn's perianal fistulas? *Dis Colon Rectum* 2007;**50**:1754-60.
92. Sciaudone G, Di Stazio C, Limongelli P*, et al.* Treatment of complex perianal fistulas in crohn disease: Infliximab, surgery or combined approach. *Can J Surg* 2010;**53**:299-304.
93. Sebastian S, Black C, Pugliese D*, et al.* The role of multimodal treatment in crohn's disease patients with perianal fistula: A multicentre retrospective cohort study. *Aliment Pharmacol Ther* 2018;**48**:941-50.
94. van der Hagen SJ, Baeten CG, Soeters PB*, et al.* Anti-tnf-alpha (infliximab) used as induction treatment in case of active proctitis in a multistep strategy followed by definitive surgery of complex anal fistulas in crohn's disease: A preliminary report. *Dis Colon Rectum* 2005;**48**:758-67.
95. Kaminski JP, Zaghiyan K, Fleshner P. Increasing experience of ligation of the intersphincteric fistula tract for patients with crohn's disease: What have we learned? *Colorectal Dis* 2017;**19**:750-5.
96. Laland M, Francois M, D'Amico F*, et al.* Identification of the optimal medical and surgical management for patients with perianal fistulising crohn's disease. *Colorectal Dis* 2023;**25**:75-82.
97. Abramowitz L, Brochard C, Pigot F*, et al.* Surgical closure, mainly with glue injection and anti-tumour necrosis factor alpha, in fistulizing perianal crohn's disease: A multicentre randomized controlled trial. *Colorectal Dis* 2022;**24**:210-9.
98. Meima-van Praag EM, van Rijn KL, Wasmann K*, et al.* Short-term anti-tnf therapy with surgical closure versus anti-tnf therapy in the treatment of perianal fistulas in crohn's disease (pisa-ii): A patient preference randomised trial. *Lancet Gastroenterol Hepatol* 2022;**7**:617-26.

Accepted Manuscript

Downloaded from https://academic.oup.com/ecco-jcc/advance-article/doi/10.1093/ecco-jcc/jjae089/7693896 by KU Leuven Libraries user on 04 July 2024

99. Meima-van Praag EM, Becker MAJ, van Rijn KL*, et al.* Short-term anti-tnf therapy with surgical closure versus anti-tnf therapy alone for crohn's perianal fistulas (pisa-ii): Long-term outcomes of an international, multicentre patient preference, randomised controlled trial. *EClinicalMedicine* 2023;**61**:102045.
100. Bislenghi G, Wolthuis A, Van Assche G*, et al.* Cx601 (darvadstrocel) for the treatment of perianal fistulizing crohn's disease. *Expert Opin Biol Ther* 2019;**19**:607-16.
101. Panes J, Garcia-Olmo D, Van Assche G*, et al.* Long-term efficacy and safety of stem cell therapy (cx601) for complex perianal fistulas in patients with crohn's disease. *Gastroenterology* 2018;**154**:1334-42 e4.
102. Garcia-Olmo D, Gilaberte I, Binek M*, et al.* Follow-up study to evaluate the long-term safety and efficacy of darvadstrocel (mesenchymal stem cell treatment) in patients with perianal fistulizing crohn's disease: Admire-cd phase 3 randomized controlled trial. *Dis Colon Rectum* 2022;**65**:713-20.
103. Lightner AL, Wang Z, Zubair AC, Dozois EJ. A systematic review and meta-analysis of mesenchymal stem cell injections for the treatment of perianal crohn's disease: Progress made and future directions. *Dis Colon Rectum* 2018;**61**:629-40.
104. Takeda. Study to assess efficacy and safety of cx601, adult allogeneic expanded adipose-derived stem cells (easc) for the treatment of complex perianal fistula(s) in participants with crohn's disease (admire-cd-ii). ClinicalTrials.Gov, 2017.
105. Cheng F, Huang Z, Li Z. Efficacy and safety of mesenchymal stem cells in treatment of complex perianal fistulas: A meta-analysis. *Stem Cells Int* 2020;**2020**:8816737.
106. Dietz AB, Dozois EJ, Fletcher JG*, et al.* Autologous mesenchymal stem cells, applied in a bioabsorbable matrix, for treatment of perianal fistulas in patients with crohn's disease. *Gastroenterology* 2017;**153**:59-62 e2.
107. Dige A, Hougaard HT, Agnholt J*, et al.* Efficacy of injection of freshly collected autologous adipose tissue into perianal fistulas in patients with crohn's disease. *Gastroenterology* 2019;**156**:2208-16 e1.
108. Dozois EJ, Lightner AL, Dietz AB*, et al.* Durable response in patients with refractory fistulizing perianal crohn's disease using autologous mesenchymal stem cells on a dissolvable matrix: Results from the phase i stem cell on matrix plug trial. *Dis Colon Rectum* 2023;**66**:243-52.
109. Herreros MD, Garcia-Olmo D, Guadalajara H*, et al.* Stem cell therapy: A compassionate use program in perianal fistula. *Stem Cells Int* 2019;**2019**:6132340.
110. Park MY, Yoon YS, Lee JL*, et al.* Comparative perianal fistula closure rates following autologous adipose tissue-derived stem cell transplantation or treatment with anti-tumor necrosis factor agents after seton placement in patients with crohn's disease: A retrospective observational study. *Stem Cell Res Ther* 2021;**12**:401.
111. Wainstein C, Quera R, Fluxa D*, et al.* Stem cell therapy in refractory perineal crohn's disease: Long-term follow-up. *Colorectal Dis* 2018.
112. Laureti S, Gionchetti P, Cappelli A*, et al.* Refractory complex crohn's perianal fistulas: A role for autologous microfragmented adipose tissue injection. *Inflamm Bowel Dis* 2020;**26**:321-30.
113. Sands BE, Blank MA, Patel K, van Deventer SJ, Study AI. Long-term treatment of rectovaginal fistulas in crohn's disease: Response to infliximab in the accent ii study. *Clin Gastroenterol Hepatol* 2004;**2**:912-20.

Accepted Manuscript

Downloaded from https://academic.oup.com/ecco-jcc/advance-article/doi/10.1093/ecco-jcc/jjae089/7693896 by KU Leuven Libraries user on 04 July 2024

114. Le Baut G, Peyrin-Biroulet L, Bouguen G*, et al.* Anti-tnf therapy for genital fistulas in female patients with crohn's disease: A nationwide study from the groupe d'etude therapeutique des affections inflammatoires du tube digestif (getaid). *Aliment Pharmacol Ther* 2018;**48**:831-8.
115. Otero-Pineiro AM, Jia X, Pedersen KE*, et al.* Surgical intervention is effective for the treatment of crohn's-related rectovaginal fistulas: Experience from a tertiary inflammatory bowel disease practice. *J Crohns Colitis* 2023;**17**:396-403.
116. Iglay K, Bennett D, Kappelman MD*, et al.* A systematic review of the patient burden of crohn's disease-related rectovaginal and anovaginal fistulas. *BMC Gastroenterol* 2022;**22**:36.
117. Singh S, Ding NS, Mathis KL*, et al.* Systematic review with meta-analysis: Faecal diversion for management of perianal crohn's disease. *Aliment Pharmacol Ther* 2015;**42**:783-92.
118. Rehg KL, Sanchez JE, Krieger BR, Marcet JE. Fecal diversion in perirectal fistulizing crohn's disease is an underutilized and potentially temporary means of successful treatment. *Am Surg* 2009;**75**:715-8.
119. Hong MK, Craig Lynch A, Bell S*, et al.* Faecal diversion in the management of perianal crohn's disease. *Colorectal Dis* 2011;**13**:171-6.
120. Gu J, Valente MA, Remzi FH, Stocchi L. Factors affecting the fate of faecal diversion in patients with perianal crohn's disease. *Colorectal Dis* 2015;**17**:66-72.
121. Kasparek MS, Glatzle J, Temeltcheva T*, et al.* Long-term quality of life in patients with crohn's disease and perianal fistulas: Influence of fecal diversion. *Dis Colon Rectum* 2007;**50**:2067-74.
122. Jew M, Meserve J, Eisenstein S*, et al.* Temporary faecal diversion for refractory perianal and/or distal colonic crohn's disease in the biologic era: An updated systematic review with meta-analysis. *J Crohns Colitis* 2023.
123. McKee RF, Keenan RA. Perianal crohn's disease--is it all bad news? *Dis Colon Rectum* 1996;**39**:136-42.
124. Regimbeau JM, Panis Y, Marteau P, Benoist S, Valleur P. Surgical treatment of anoperineal crohn's disease: Can abdominoperineal resection be predicted? *J Am Coll Surg* 1999;**189**:171-6.
125. Schlegel N, Kim M, Reibetanz J*, et al.* Sphincter-sparing intersphincteric rectal resection as an alternative to proctectomy in long-standing fistulizing and stenotic crohn's proctitis? *Int J Colorectal Dis* 2015;**30**:655-63.
126. Williams JG, Hughes LE. Abdominoperineal resection for severe perianal crohn's disease. *Dis Colon Rectum* 1990;**33**:402-7.
127. Hollis RH, Smith N, Sapci I*, et al.* Small bowel crohn's disease recurrence is common after total proctocolectomy for crohn's colitis. *Dis Colon Rectum* 2022;**65**:390-8.
128. Lightner AL, Steele SR, Delaney CP*, et al.* Colonic disease recurrence following proctectomy with end colostomy for anorectal crohn's disease. *Colorectal Dis* 2021;**23**:2425-35.
129. Li W, Stocchi L, Elagili F, Kiran RP, Strong SA. Healing of the perineal wound after proctectomy in crohn's disease patients: Only preoperative perineal sepsis predicts poor outcome. *Tech Coloproctol* 2017;**21**:715-20.
130. McGarity WC, Mallory C, Walker J. Perineal wound healing after abdominoperineal resection. *Am Surg* 1976;**42**:206-11.

Accepted Manuscript

Downloaded from https://academic.oup.com/ecco-jcc/advance-article/doi/10.1093/ecco-jcc/jjae089/7693896 by KU Leuven Libraries user on 04 July 2024

131. Schaden D, Schauer G, Haas F, Berger A. Myocutaneous flaps and proctocolectomy in severe perianal crohn's disease--a single stage procedure. *Int J Colorectal Dis* 2007;**22**:1453-7.
132. Waits JO, Dozois RR, Kelly KA. Primary closure and continuous irrigation of the perineal wound after proctectomy. *Mayo Clin Proc* 1982;**57**:185-8.
133. Lansdorp CA, Buskens CJ, Gecse KB, D'Haens GR, Van Hulst RA. Wound healing of metastatic perineal crohn's disease using hyperbaric oxygen therapy: A case series. *United European Gastroenterol J* 2020;**8**:820-7.
134. Geldof J, Iqbal N, LeBlanc JF*, et al.* Classifying perianal fistulising crohn's disease: An expert consensus to guide decision-making in daily practice and clinical trials. *Lancet Gastroenterol Hepatol* 2022;**7**:576-84.
135. de Groof EJ, Cabral VN, Buskens CJ*, et al.* Systematic review of evidence and consensus on perianal fistula: An analysis of national and international guidelines. *Colorectal Dis* 2016;**18**:O119-34.
136. Singh S, Al-Darmaki A, Frolkis AD*, et al.* Postoperative mortality among patients with inflammatory bowel diseases: A systematic review and meta-analysis of population-based studies. *Gastroenterology* 2015;**149**:928-37.
137. Udholm LS, Rasmussen SL, Madsbøll TK, Omairi M, El-Hussuna A. A systemic review and metaanalysis of postoperative outcomes in urgent and elective bowel resection in patients with crohn's disease. *Int J Colorectal Dis* 2021;**36**:253-63.
138. Risk factors for unfavourable postoperative outcome in patients with crohn's disease undergoing right hemicolectomy or ileocaecal resection an international audit by escp and s-ecco. *Colorectal Dis* 2017.
139. El-Hussuna A, Karer MLM, Uldall Nielsen NN*, et al.* Postoperative complications and waiting time for surgical intervention after radiologically guided drainage of intra-abdominal abscess in patients with crohn's disease. *BJS Open* 2021;**5**.
140. Celentano V, Giglio MC, Pellino G*, et al.* High complication rate in crohn's disease surgery following percutaneous drainage of intra-abdominal abscess: A multicentre study. *Int J Colorectal Dis* 2022;**37**:1421-8.
141. Sakurai Kimura CM, Scanavini Neto A, Queiroz NSF*, et al.* Abdominal surgery in crohn's disease: Risk factors for complications. *Inflamm Intest Dis* 2021;**6**:18-24.
142. Fahim M, Dijksman LM, Derksen WJM*, et al.* Prospective multicentre study of a new bowel obstruction treatment in colorectal surgery: Reduced morbidity and mortality. *Eur J Surg Oncol* 2021;**47**:2414-20.
143. Liu R-Q, Qiao S-H, Wang K-H*, et al.* Prospective evaluation of intestinal decompression in treatment of acute bowel obstruction from crohn's disease. *Gastroenterology report* 2019;**7**:263-71.
144. Sebastian S, Segal JP, Hedin C*, et al.* Ecco topical review: Roadmap to optimal peri-operative care in ibd. *J Crohns Colitis* 2023;**17**:153-69.
145. Adamina M, Gerasimidis K, Sigall-Boneh R*, et al.* Perioperative dietary therapy in inflammatory bowel disease. *J Crohns Colitis* 2020;**14**:431-44.
146. Clancy C, Boland T, Deasy J, McNamara D, Burke JP. A meta-analysis of percutaneous drainage versus surgery as the initial treatment of crohn's disease-related intra-abdominal abscess. *J Crohns Colitis* 2016;**10**:202-8.
147. El-Hussuna A, Steenholdt C, Merrild Karer ML*, et al.* Watchful waiting after radiological guided drainage of intra-abdominal abscess in patients with crohn's

Accepted Manuscript

Downloaded from https://academic.oup.com/ecco-jcc/advance-article/doi/10.1093/ecco-jcc/jjae089/7693896 by KU Leuven Libraries user on 04 July 2024

disease might be associated with increased rates of stoma construction. *Crohn's & Colitis 360* 2023;**5**.
148. Waked B, Holvoet T, Geldof J*, et al.* Conservative management of spontaneous intra-abdominal abscess in crohn's disease: Outcome and prognostic factors. *J Dig Dis* 2021;**22**:263-70.
149. Huang W, Tang Y, Nong L, Sun Y. Risk factors for postoperative intra-abdominal septic complications after surgery in crohn's disease: A meta-analysis of observational studies. *J Crohns Colitis* 2015;**9**:293-301.
150. da Luz Moreira A, Stocchi L, Tan E, Tekkis PP, Fazio VW. Outcomes of crohn's disease presenting with abdominopelvic abscess. *Dis Colon Rectum* 2009;**52**:906-12.
151. Luong TV, Grandt SD, Negoi I, Palubinskas S, El-Hussuna A. Preoperative factors associated with prolonged postoperative in-hospital length of stay in patients with crohn's disease undergoing intestinal resection or strictureplasty. *Int J Colorectal Dis* 2019;**34**:1925-31.
152. He X, Lin X, Lian L*, et al.* Preoperative percutaneous drainage of spontaneous intra-abdominal abscess in patients with crohn's disease: A meta-analysis. *J Clin Gastroenterol* 2015;**49**:e82-90.
153. Peyser DK, Carmichael H, Dean A*, et al.* Early versus delayed ileocolic resection for complicated crohn's disease: Is "cooling off" necessary? *Surg Endosc* 2022;**36**:4290-8.
154. Bettenworth D, Gustavsson A, Atreja A*, et al.* A pooled analysis of efficacy, safety, and long-term outcome of endoscopic balloon dilation therapy for patients with stricturing crohn's disease. *Inflamm Bowel Dis* 2017;**23**:133-42.
155. Hassan C, Zullo A, De Francesco V*, et al.* Systematic review: Endoscopic dilatation in crohn's disease. *Alimentary pharmacology & therapeutics* 2007;**26**:1457-64.
156. Morar PS, Faiz O, Warusavitarne J*, et al.* Systematic review with meta-analysis: Endoscopic balloon dilatation for crohn's disease strictures. *Aliment Pharmacol Ther* 2015;**42**:1137-48.
157. Navaneethan U, Lourdusamy V, Njei B, Shen B. Endoscopic balloon dilation in the management of strictures in crohn's disease: A systematic review and meta-analysis of non-randomized trials. *Surg Endosc* 2016;**30**:5434-43.
158. Andújar X, Loras C, González B*, et al.* Efficacy and safety of endoscopic balloon dilation in inflammatory bowel disease: Results of the large multicenter study of the eneida registry. *Surg Endosc* 2020;**34**:1112-22.
159. Bamba S, Sakemi R, Fujii T*, et al.* A nationwide, multi-center, retrospective study of symptomatic small bowel stricture in patients with crohn's disease. *J Gastroenterol* 2020;**55**:615-26.
160. Uda A, Kuwabara H, Shimizu S, Iwakiri R, Fushimi K. Optimal use of biologics with endoscopic balloon dilatation for repeated intestinal strictures in crohn's disease. *JGH Open* 2020;**4**:532-40.
161. Lu C, Baraty B, Lee Robertson H*, et al.* Systematic review: Medical therapy for fibrostenosing crohn's disease. *Aliment Pharmacol Ther* 2020;**51**:1233-46.
162. Bettenworth D, Bokemeyer A, Kou L*, et al.* Systematic review with meta-analysis: Efficacy of balloon-assisted enteroscopy for dilation of small bowel crohn's disease strictures. *Aliment Pharmacol Ther* 2020;**52**:1104-16.

Accepted Manuscript

Downloaded from https://academic.oup.com/ecco-jcc/advance-article/doi/10.1093/ecco-jcc/jjae089/7693896 by KU Leuven Libraries user on 04 July 2024

163. Costa-Santos MP, Palmela C, Torres J*, et al.* Preoperative enteral nutrition in adults with complicated crohn's disease: Effect on disease outcomes and gut microbiota. *Nutrition* 2020;**70s**:100009.
164. Ge X, Tang S, Yang X*, et al.* The role of exclusive enteral nutrition in the preoperative optimization of laparoscopic surgery for patients with crohn's disease: A cohort study. *Int J Surg* 2019;**65**:39-44.
165. Rocha A, Bessa I, Lago P*, et al.* Preoperative enteral nutrition and surgical outcomes in adults with crohn's disease: A systematic review. *GE Port J Gastroenterol* 2019;**26**:184-95.
166. Gordon-Dixon A, Gore-Rodney J, Hampal R*, et al.* The role of exclusive enteral nutrition in the pre-operative optimisation of adult patients with crohn's disease. A systematic review. *Clin Nutr ESPEN* 2021;**46**:99-105.
167. Jiang T, Jiang Y, Jin Q*, et al.* Role of perioperative nutritional status and enteral nutrition in predicting and preventing post-operative complications in patients with crohn's disease. *Front Nutr* 2022;**9**:1085037.
168. Meade S, Patel KV, Luber RP*, et al.* A retrospective cohort study: Pre-operative oral enteral nutritional optimisation for crohn's disease in a uk tertiary ibd centre. *Aliment Pharmacol Ther* 2022;**56**:646-63.
169. Brennan GT, Ha I, Hogan C*, et al.* Does preoperative enteral or parenteral nutrition reduce postoperative complications in crohn's disease patients: A meta-analysis. *Eur J Gastroenterol Hepatol* 2018;**30**:997-1002.
170. Traiki TAB, Alshammari SA, Aljomah NA*, et al.* The impact of preoperative total parenteral nutrition on the surgical complications of crohn's disease: A retrospective cohort study. *Saudi J Gastroenterol* 2023;**29**:158-63.
171. Abdalla S, Benoist S, Maggiori L*, et al.* Impact of preoperative enteral nutritional support on postoperative outcome in patients with crohn's disease complicated by malnutrition: Results of a subgroup analysis of the nationwide cohort registry from the getaid chirurgie group. *Colorectal Dis* 2021;**23**:1451-62.
172. Gionchetti P, Dignass A, Danese S*, et al.* 3rd european evidence-based consensus on the diagnosis and management of crohn's disease 2016: Part 2: Surgical management and special situations. *J Crohns Colitis* 2017;**11**:135-49.
173. Law CC, Bell C, Koh D*, et al.* Risk of postoperative infectious complications from medical therapies in inflammatory bowel disease. *Cochrane Database Syst Rev* 2020;**10**:Cd013256.
174. Subramanian V, Saxena S, Kang JY, Pollok RC. Preoperative steroid use and risk of postoperative complications in patients with inflammatory bowel disease undergoing abdominal surgery. *Am J Gastroenterol* 2008;**103**:2373-81.
175. Abou Khalil M, Abou-Khalil J, Motter J*, et al.* Immunosuppressed patients with crohn's disease are at increased risk of postoperative complications: Results from the acs-nsqip database. *J Gastrointest Surg* 2019;**23**:1188-97.
176. Freund MR, Emile SH, Horesh N*, et al.* Redo ileocolic resection for recurrent crohn’s disease: A review and meta-analysis of surgical outcomes. *Surgery* 2022;**172**:1614-21.
177. Quaresma AB, Yamamoto T, Kotze PG. Biologics and surgical outcomes in crohn's disease: Is there a direct relationship? *Therap Adv Gastroenterol* 2020;**13**:1756284820931738.

Accepted Manuscript

Downloaded from https://academic.oup.com/ecco-jcc/advance-article/doi/10.1093/ecco-jcc/jjae089/7693896 by KU Leuven Libraries user on 04 July 2024

178. Cohen BL, Fleshner P, Kane SV*, et al.* Prospective cohort study to investigate the safety of preoperative tumor necrosis factor inhibitor exposure in patients with inflammatory bowel disease undergoing intra-abdominal surgery. *Gastroenterology* 2022;**163**:204-21.
179. Law CCY, Narula A, Lightner AL*, et al.* Systematic review and meta-analysis: Preoperative vedolizumab treatment and postoperative complications in patients with inflammatory bowel disease. *J Crohns Colitis* 2018;**12**:538-45.
180. Moosvi Z, Duong JT, Bechtold ML, Nguyen DL. Systematic review and meta-analysis: Preoperative vedolizumab and postoperative complications in patients with ibd. *South Med J* 2021;**114**:98-105.
181. Yung DE, Horesh N, Lightner AL*, et al.* Systematic review and meta-analysis: Vedolizumab and postoperative complications in inflammatory bowel disease. *Inflammatory Bowel Diseases* 2018;**24**:2327-38.
182. Guo D, Jiang K, Hong J*, et al.* Association between vedolizumab and postoperative complications in ibd: A systematic review and meta-analysis. *Int J Colorectal Dis* 2021;**36**:2081-92.
183. Garg R, Mohan BP, Ponnada S*, et al.* Postoperative outcomes after preoperative ustekinumab exposure in patients with crohn's disease: A systematic review and meta-analysis. *Annals of gastroenterology* 2021;**34**:691-8.
184. Lightner AL, McKenna NP, Tse CS*, et al.* Postoperative outcomes in ustekinumab-treated patients undergoing abdominal operations for crohn's disease. *J Crohns Colitis* 2018;**12**:402-7.
185. Adamina M, Gie O, Demartines N, Ris F. Contemporary perioperative care strategies. *Br J Surg* 2013;**100**:38-54.
186. Zangenberg MS, Horesh N, Kopylov U, El-Hussuna A. Preoperative optimization of patients with inflammatory bowel disease undergoing gastrointestinal surgery: A systematic review. *Int J Colorectal Dis* 2017;**32**:1663-76.
187. Barnes EL, Lightner AL, Regueiro M. Peri-operative and post-operative management of patients with crohn's disease and ulcerative colitis. *Clin Gastroenterol Hepatol* 2019.
188. Dasari BV, McKay D, Gardiner K. Laparoscopic versus open surgery for small bowel crohn's disease. *Cochrane Database Syst Rev* 2011:CD006956.
189. Tan JJ, Tjandra JJ. Laparoscopic surgery for crohn's disease: A meta-analysis. *Dis Colon Rectum* 2007;**50**:576-85.
190. Patel SV, Patel SV, Ramagopalan SV, Ott MC. Laparoscopic surgery for crohn's disease: A meta-analysis of perioperative complications and long term outcomes compared with open surgery. *BMC Surg* 2013;**13**:14.
191. Shigeta K, Okabayashi K, Hasegawa H*, et al.* Meta-analysis of laparoscopic surgery for recurrent crohn's disease. *Surg Today* 2016;**46**:970-8.
192. Ponsioen CY, de Groof EJ, Eshuis EJ*, et al.* Laparoscopic ileocaecal resection versus infliximab for terminal ileitis in crohn's disease: A randomised controlled, open-label, multicentre trial. *Lancet Gastroenterol Hepatol* 2017;**2**:785-92.
193. Stevens TW, Haasnoot ML, D'Haens GR*, et al.* Laparoscopic ileocaecal resection versus infliximab for terminal ileitis in crohn's disease: Retrospective long-term follow-up of the lir!C trial. *Lancet Gastroenterol Hepatol* 2020;**5**:900-7.

Accepted Manuscript

Downloaded from https://academic.oup.com/ecco-jcc/advance-article/doi/10.1093/ecco-jcc/jjae089/7693896 by KU Leuven Libraries user on 04 July 2024

194. Ryan É J, Orsi G, Boland MR*, et al.* Meta-analysis of early bowel resection versus initial medical therapy in patient's with ileocolonic crohn's disease. *Int J Colorectal Dis* 2020;**35**:501-12.
195. Simillis C, Purkayastha S, Yamamoto T*, et al.* A meta-analysis comparing conventional end-to-end anastomosis vs. Other anastomotic configurations after resection in crohn's disease. *Dis Colon Rectum* 2007;**50**:1674-87.
196. Guo Z, Li Y, Zhu W*, et al.* Comparing outcomes between side-to-side anastomosis and other anastomotic configurations after intestinal resection for patients with crohn's disease: A meta-analysis. *World J Surg* 2013;**37**:893-901.
197. He X, Chen Z, Huang J*, et al.* Stapled side-to-side anastomosis might be better than handsewn end-to-end anastomosis in ileocolic resection for crohn's disease: A meta-analysis. *Dig Dis Sci* 2014;**59**:1544-51.
198. Feng JS, Li JY, Yang Z*, et al.* Stapled side-to-side anastomosis might be benefit in intestinal resection for crohn's disease: A systematic review and network meta-analysis. *Medicine (Baltimore)* 2018;**97**:e0315.
199. Kellil T, Chaouch MA, Guedich A*, et al.* Surgical features to reduce anastomotic recurrence of crohn's disease that requires reoperation: A systematic review. *Surg Today* 2022;**52**:542-9.
200. Thin LWY, Picardo S, Sooben S*, et al.* Ileocolonic end-to-end anastomoses in crohn's disease increase the risk of early post-operative endoscopic recurrence in those undergoing an emergency resection. *J Gastrointest Surg* 2021;**25**:241-51.
201. Zhou J, Li Y, Gong J, Zhu W. Frequency and risk factors of surgical recurrence of crohn's disease after primary bowel resection. *Turk J Gastroenterol* 2018;**29**:655-63.
202. Celentano V, Pellino G, Spinelli A*, et al.* Anastomosis configuration and technique following ileocaecal resection for crohn's disease: A multicentre study. *Updates Surg* 2021;**73**:149-56.
203. Kono T, Ashida T, Ebisawa Y*, et al.* A new antimesenteric functional end-to-end handsewn anastomosis: Surgical prevention of anastomotic recurrence in crohn's disease. *Dis Colon Rectum* 2011;**54**:586-92.
204. Kono T, Fichera A, Maeda K*, et al.* Kono-s anastomosis for surgical prophylaxis of anastomotic recurrence in crohn's disease: An international multicenter study. *J Gastrointest Surg* 2016;**20**:783-90.
205. Horisberger K, Birrer DL, Rickenbacher A, Turina M. Experiences with the kono-s anastomosis in crohn's disease of the terminal ileum-a cohort study. *Langenbecks Arch Surg* 2021;**406**:1173-80.
206. Shimada N, Ohge H, Kono T*, et al.* Surgical recurrence at anastomotic site after bowel resection in crohn's disease: Comparison of kono-s and end-to-end anastomosis. *J Gastrointest Surg* 2019;**23**:312-9.
207. Fichera A, Mangrola AM, Olortegui KS*, et al.* Long-term outcomes of the kono-s anastomosis: A multicenter study. *Dis Colon Rectum* 2024;**67**:406-13.
208. Luglio G, Rispo A, Imperatore N*, et al.* Surgical prevention of anastomotic recurrence by excluding mesentery in crohn's disease: The supreme-cd study - a randomized clinical trial. *Ann Surg* 2020;**272**:210-7.
209. Alshantti A, Hind D, Hancock L, Brown SR. The role of kono-s anastomosis and mesenteric resection in reducing recurrence after surgery for crohn's disease: A systematic review. *Colorectal Dis* 2021;**23**:7-17.

Accepted Manuscript

Downloaded from https://academic.oup.com/ecco-jcc/advance-article/doi/10.1093/ecco-jcc/jjae089/7693896 by KU Leuven Libraries user on 04 July 2024

210. Ng CH, Chin YH, Lin SY*, et al.* Kono-s anastomosis for crohn's disease: A systemic review, meta-analysis, and meta-regression. *Surg Today* 2021;**51**:493-501.
211. Tyrode G, Lakkis Z, Vernerey D*, et al.* Kono-s anastomosis is not superior to conventional anastomosis for the reduction of postoperative endoscopic recurrence in crohn's disease. *Inflammatory Bowel Diseases* 2023.
212. (AMC-UvA) AMC-UvA. Comparing hand-sewn (end-to-end or kono-s) to stapled anastomosis in ileocolic resection for crohn's disease (end2end). 2023 edn. ClinicalTrials.gov, 2023.
213. University WMCoC. Study of the kono-s anastomosis versus the side-to-side functional end anastomosis. ClinicalTrials.Gov, 2014.
214. Haanappel AEG, Bellato V, Buskens CJ*, et al.* Optimising surgical anastomosis in ileocolic resection for crohn's disease with respect to recurrence and functionality: Two international parallel randomized controlled trials comparing handsewn (end-to-end or kono-s) to stapled anastomosis (hand2end and the end2end studies). *BMC Surg* 2024;**24**:71.
215. Coffey CJ, Kiernan MG, Sahebally SM*, et al.* Inclusion of the mesentery in ileocolic resection for crohn's disease is associated with reduced surgical recurrence. *J Crohns Colitis* 2018;**12**:1139-50.
216. Myrelid P, Soderholm JD, Olaison G, Sjodahl R, Andersson P. Split stoma in resectional surgery of high-risk patients with ileocolonic crohn's disease. *Colorectal Dis* 2012;**14**:188-93.
217. Aberra FN, Lewis JD, Hass D*, et al.* Corticosteroids and immunomodulators: Postoperative infectious complication risk in inflammatory bowel disease patients. *Gastroenterology* 2003;**125**:320-7.
218. Rizzo G, Armuzzi A, Pugliese D*, et al.* Anti-tnf-alpha therapies do not increase early postoperative complications in patients with inflammatory bowel disease. An italian single-center experience. *Int J Colorectal Dis* 2011;**26**:1435-44.
219. Rottoli M, Vallicelli C, Ghignone F*, et al.* Predictors of early recurrence after strictureplasty for crohn's disease of the small bowel during the years of biologics. *Digestive and liver disease : official journal of the Italian Society of Gastroenterology and the Italian Association for the Study of the Liver* 2019;**51 5**:663-8.
220. Rottoli M, Tanzanu M, Manzo CA*, et al.* Strictureplasty for crohn's disease of the small bowel in the biologic era: Long-term outcomes and risk factors for recurrence. *Tech Coloproctol* 2020;**24**:711-20.
221. Bislenghi G, Sucameli F, Fieuws S*, et al.* Non-conventional versus conventional strictureplasties for crohn's disease. A systematic review and meta-analysis of treatment outcomes. *J Crohns Colitis* 2022;**16**:319-30.
222. Reese GE, Purkayastha S, Tilney HS*, et al.* Strictureplasty vs resection in small bowel crohn's disease: An evaluation of short-term outcomes and recurrence. *Colorectal Dis* 2007;**9**:686-94.
223. Butt WT, Ryan É J, Boland MR*, et al.* Strictureplasty versus bowel resection for the surgical management of fibrostenotic crohn's disease: A systematic review and meta-analysis. *Int J Colorectal Dis* 2020;**35**:705-17.
224. Tekkis PP, Purkayastha S, Lanitis S*, et al.* A comparison of segmental vs subtotal/total colectomy for colonic crohn's disease: A meta-analysis. *Colorectal disease : the*

Accepted Manuscript

Downloaded from https://academic.oup.com/ecco-jcc/advance-article/doi/10.1093/ecco-jcc/jjae089/7693896 by KU Leuven Libraries user on 04 July 2024

official journal of the Association of Coloproctology of Great Britain and Ireland 2006;**8**:82-90.

225. Angriman I, Pirozzolo G, Bardini R*, et al.* A systematic review of segmental vs subtotal colectomy and subtotal colectomy vs total proctocolectomy for colonic crohn's disease. *Colorectal disease : the official journal of the Association of Coloproctology of Great Britain and Ireland* 2017;**19**:e279-e87.
226. Collaborative SCsoCsds. Surgical treatment of colonic crohn ' s disease : A national snapshot study. *Langenbeck's Archives of Surgery* 2020;**406**:1165-72.
227. Pellino G, Rottoli M, Mineccia M*, et al.* Segmental versus total colectomy for crohn's disease in the biologic era: Results from the scotch international, multicentric study. *Journal of Crohn's and Colitis* 2022;**16**:1853-61.
228. Scaringi S, Di Bella A, Boni L*, et al.* New perspectives on the long-term outcome of segmental colectomy for crohn's colitis: An observational study on 200 patients. *Int J Colorectal Dis* 2018;**33**:479-85.
229. Annese V, Beaugerie L, Egan L*, et al.* European evidence-based consensus: Inflammatory bowel disease and malignancies. *J Crohns Colitis* 2015;**9**:945-65.
230. Pedersen N, Duricova D, Elkjaer M*, et al.* Risk of extra-intestinal cancer in inflammatory bowel disease: Meta-analysis of population-based cohort studies. *Am J Gastroenterol* 2010;**105**:1480-7.
231. Lutgens MW, van Oijen MG, van der Heijden GJ*, et al.* Declining risk of colorectal cancer in inflammatory bowel disease: An updated meta-analysis of population-based cohort studies. *Inflamm Bowel Dis* 2013;**19**:789-99.
232. Ording AG, Horváth-Puhó E, Erichsen R*, et al.* Five-year mortality in colorectal cancer patients with ulcerative colitis or crohn's disease: A nationwide population-based cohort study. *Inflammatory Bowel Diseases* 2013;**19**:800–5.
233. Ali RA, Dooley C, Comber H, Newell J, Egan LJ. Clinical features, treatment, and survival of patients with colorectal cancer with or without inflammatory bowel disease. *Clin Gastroenterol Hepatol* 2011;**9**:584-9.e1-2.
234. Mescoli C, Albertoni L, D'Incá R, Rugge M. Dysplasia in inflammatory bowel diseases. *Dig Liver Dis* 2013;**45**:186-94.
235. Neri B, Mancone R, Savino L*, et al.* Mucinous and signet-ring cell colonic adenocarcinoma in inflammatory bowel disease: A case-control study. *Cancers (Basel)* 2023;**15**.
236. Kiran RP, Nisar PJ, Goldblum JR*, et al.* Dysplasia associated with crohn's colitis: Segmental colectomy or more extended resection? *Ann Surg* 2012;**256**:221-6.
237. Maser EA, Sachar DB, Kruse D*, et al.* High rates of metachronous colon cancer or dysplasia after segmental resection or subtotal colectomy in crohn's colitis. *Inflamm Bowel Dis* 2013;**19**:1827-32.
238. Olén O, Erichsen R, Sachs MC*, et al.* Colorectal cancer in crohn's disease: A scandinavian population-based cohort study. *Lancet Gastroenterol Hepatol* 2020;**5**:475-84.
239. Sensi B, Khan J, Warusavitarne J*, et al.* Long-term oncological outcome of segmental versus extended colectomy for colorectal cancer in crohn's disease: Results from an international multicentre study. *J Crohns Colitis* 2022;**16**:954-62.

Accepted Manuscript

Downloaded from https://academic.oup.com/ecco-jcc/advance-article/doi/10.1093/ecco-jcc/jjae089/7693896 by KU Leuven Libraries user on 04 July 2024

240. Bogach J, Pond G, Eskicioglu C, Simunovic M, Seow H. Extent of surgical resection in inflammatory bowel disease associated colorectal cancer: A population-based study. *Journal of Gastrointestinal Surgery* 2021;**25**:2610-8.
241. Connelly TM, Koltun WA. The surgical treatment of inflammatory bowel disease-associated dysplasia. *Expert Rev Gastroenterol Hepatol* 2013;**7**:307-21; quiz 22.
242. Van Cutsem E, Nordlinger B, Cervantes A. Advanced colorectal cancer: Esmo clinical practice guidelines for treatment. *Ann Oncol* 2010;**21 Suppl 5**:v93-7.
243. Lovasz BD, Lakatos L, Golovics PA*, et al.* Risk of colorectal cancer in crohn's disease patients with colonic involvement and stenosing disease in a population-based cohort from hungary. *J Gastrointestin Liver Dis* 2013;**22**:265-8.
244. Uzzan M, Stefanescu C, Maggiori L*, et al.* Case series: Does a combination of anti-tnf antibodies and transient ileal fecal stream diversion in severe crohn's colitis with perianal fistula prevent definitive stoma? *Am J Gastroenterol* 2013;**108**:1666-8.
245. Burman JH, Thompson H, Cooke WT, Williams JA. The effects of diversion of intestinal contents on the progress of crohn's disease of the large bowel. *Gut* 1971;**12**:11-5.
246. Edwards CM, George BD, Jewell DP*, et al.* Role of a defunctioning stoma in the management of large bowel crohn's disease. *The British journal of surgery* 2000;**87**:1063-6.
247. Harper PH, Truelove SC, Lee EC, Kettlewell MG, Jewell DP. Split ileostomy and ileocolostomy for crohn's disease of the colon and ulcerative colitis: A 20 year survey. *Gut* 1983;**24**:106-13.
248. Spivak J, Landers CJ, Vasiliauskas EA*, et al.* Antibodies to i2 predict clinical response to fecal diversion in crohn's disease. *Inflammatory bowel diseases* 2006;**12**:1122-30.
249. Bafford AC, Latushko A, Hansraj N, Jambaulikar G, Ghazi LJ. The use of temporary fecal diversion in colonic and perianal crohn's disease does not improve outcomes. *Digestive diseases and sciences* 2017;**62**:2079-86.
250. Mennigen R, Heptner B, Senninger N, Rijcken E. Temporary fecal diversion in the management of colorectal and perianal crohn's disease. *Gastroenterology research and practice* 2015;**2015**:286315-.
251. Bemelman WA, Warusavitarne J, Sampietro GM*, et al.* Ecco-escp consensus on surgery for crohn's disease. *Journal of Crohn's & colitis* 2018;**12**:1-16.
252. Chang S, Shen B, Remzi F. When not to pouch: Important considerations for patient selection for ileal pouch-anal anastomosis. *Gastroenterology & hepatology* 2017;**13**:466-75.
253. Fazio VW, Kiran RP, Remzi FH*, et al.* Ileal pouch anal anastomosis: Analysis of outcome and quality of life in 3707 patients. *Ann Surg* 2013;**257**:679-85.
254. Le Q, Melmed G, Dubinsky M*, et al.* Surgical outcome of ileal pouch-anal anastomosis when used intentionally for well-defined crohn's disease. *Inflammatory bowel diseases* 2013;**19**:30-6.
255. Manilich E, Remzi FH, Fazio VW, Church JM, Kiran RP. Prognostic modeling of preoperative risk factors of pouch failure. *Dis Colon Rectum* 2012;**55**:393-9.
256. Reese GE, Lovegrove RE, Tilney HS*, et al.* The effect of crohn's disease on outcomes after restorative proctocolectomy. *Diseases of the colon and rectum* 2007;**50**:239-50.
257. Ananthakrishnan AN, McGinley EL, Binion DG. Does it matter where you are hospitalized for inflammatory bowel disease? A nationwide analysis of hospital volume. *Am J Gastroenterol* 2008;**103**:2789-98.

Accepted Manuscript

Downloaded from https://academic.oup.com/ecco-jcc/advance-article/doi/10.1093/ecco-jcc/jjae089/7693896 by KU Leuven Libraries user on 04 July 2024

258. Williams H, Alabbadi S, Khaitov S, Egorova N, Greenstein A. Association of hospital volume with postoperative outcomes in crohn's disease. *Colorectal Disease* 2023;**25**:688-94.
259. Fiorino G, Lytras T, Younge L*, et al.* Quality of care standards in inflammatory bowel diseases: A european crohn's and colitis organisation [ecco] position paper. *Journal of Crohn's & colitis* 2020;**14**:1037-48.
260. !!! INVALID CITATION !!! 12.
261. Candia R B-SGAMHHCNGC. Colonoscopy-guided therapy for the prevention of post-operative recurrence of crohn's disease (review). *Cochrane Library* 2020.
262. De Cruz P, Kamm MA, Prideaux L, Allen PB, Desmond PV. Postoperative recurrent luminal crohn's disease: A systematic review. *Inflammatory Bowel Diseases* 2012;**18**:758-77.
263. De Cruz P, Kamm MA, Hamilton AL*, et al.* Crohn's disease management after intestinal resection: A randomised trial. *The Lancet* 2015;**385**:1406-17.
264. Schlussel AT, Cherng NB, Alavi K. *Current trends and challenges in the postoperative medical management of crohn's disease: A systematic review*: Elsevier Inc.; 2017.
265. De Cruz P, Hamilton AL, Burrell KJ*, et al.* Endoscopic prediction of crohn's disease postoperative recurrence. *Inflammatory Bowel Diseases* 2022;**28**:680-8.
266. Yamamoto T, Watanabe T. Strategies for the prevention of postoperative recurrence of crohn's disease. *Colorectal Disease* 2013;**15**:1471-80.
267. Gjuladin-Hellon T, Gordon M, Iheozor-Ejiofor Z, Akobeng AK. Oral 5-aminosalicylic acid for maintenance of surgically-induced remission in crohn's disease. *Cochrane Database Syst Rev* 2019;**6**:Cd008414.
268. Regueiro M, Feagan BG, Zou B*, et al.* Infliximab reduces endoscopic, but not clinical, recurrence of crohn's disease after ileocolonic resection. *Gastroenterology* 2016;**150**:1568-78.
269. Zhao Y, Ma T, Chen YF*, et al.* Biologics for the prevention of postoperative crohn's disease recurrence: A systematic review and meta-analysis. *Clin Res Hepatol Gastroenterol* 2015;**39**:637-49.
270. Ferrante M, Pouillon L, Mañosa M*, et al.* Results of the eighth scientific workshop of ecco: Prevention and treatment of postoperative recurrence in patients with crohn's disease undergoing an ileocolonic resection with ileocolonic anastomosis. *Journal of Crohn's and Colitis* 2023;**17**:1707-22.
271. D'Haens G, Taxonera C, Lopez-Sanroman A*, et al.* Op14 prevention of postoperative recurrence of crohn's disease with vedolizumab: First results of the prospective placebo-controlled randomised trial reprevio. *Journal of Crohn's and Colitis* 2023;**17**:i19-i.
272. Mañosa M, Fernández-Clotet A, Nos P*, et al.* Ustekinumab and vedolizumab for the prevention of postoperative recurrence of crohn's disease: Results from the eneida registry. *Dig Liver Dis* 2023;**55**:46-52.
273. Ozgur I, Kulle CB, Buyuk M*, et al.* What are the predictors for recurrence of crohn's disease after surgery? *Medicine* 2021;**100**:e25340.
274. Lee KE, Cantrell S, Shen B, Faye AS. Post-operative prevention and monitoring of crohn's disease recurrence. *Gastroenterology Report* 2022;**10**.

Accepted Manuscript

Downloaded from https://academic.oup.com/ecco-jcc/advance-article/doi/10.1093/ecco-jcc/jjae089/7693896 by KU Leuven Libraries user on 04 July 2024

275. Scarpa M, Pilon F, Pengo V*, et al.* Deep venous thrombosis after surgery for inflammatory bowel disease: Is standard dose low molecular weight heparin prophylaxis enough? *World journal of surgery* 2010;**34**:1629-36.
276. McKechnie T, Wang J, Springer JE*, et al.* Extended thromboprophylaxis following colorectal surgery in patients with inflammatory bowel disease: A comprehensive systematic clinical review. *Colorectal Disease* 2020;**22**:663-78.

Accepted Manuscript

Downloaded from https://academic.oup.com/ecco-jcc/advance-article/doi/10.1093/ecco-jcc/jjae089/7693896 by KU Leuven Libraries user on 04 July 2024

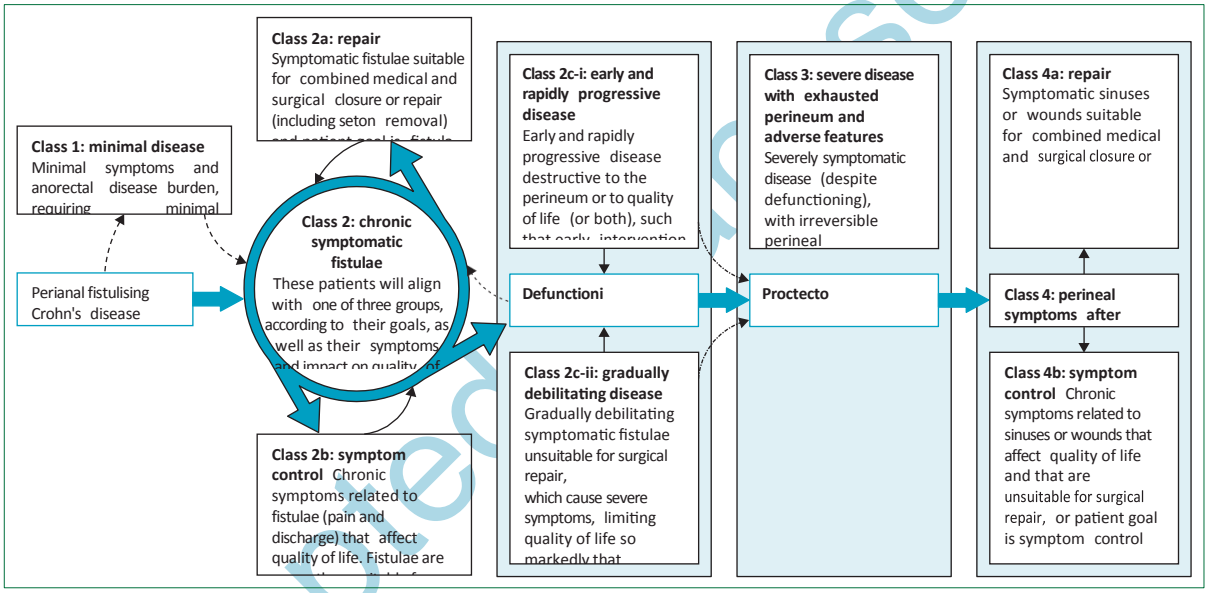
Manuscript Doi: 10.1093/ecco-jcc/jjae089

Figures

Figure 1. Classification of perianal fistulising Crohn's disease

At any moment throughout its disease course, perianal fistulising Crohn's disease can be classified into one of four classes[134]

(reprinted with permission from Elsevier, License Number 5760781248280).

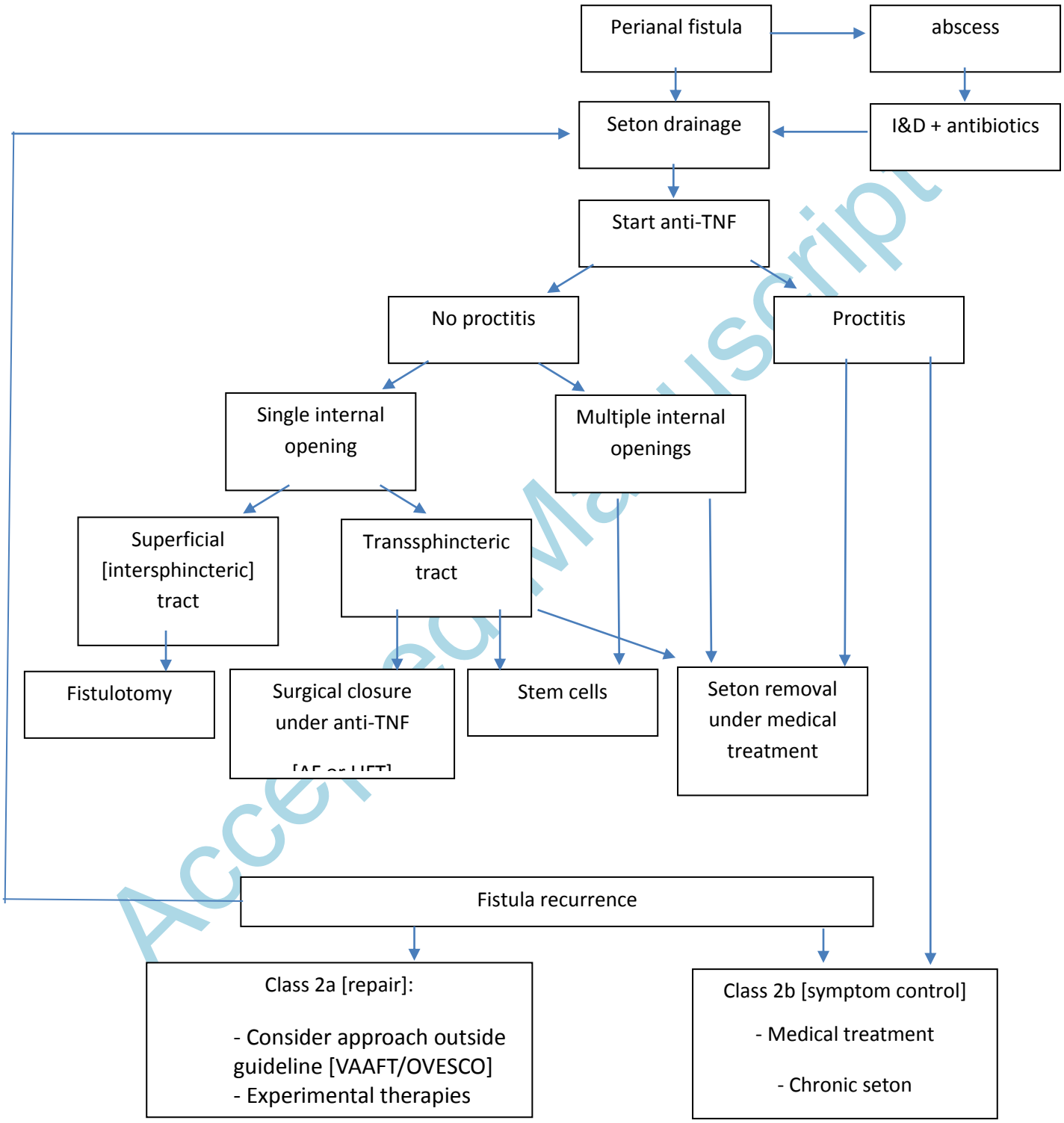


Accepted Manuscript

Downloaded from https://academic.oup.com/ecco-jcc/advance-article/doi/10.1093/ecco-jcc/jjae089/7693896 by KU Leuven Libraries user on 04 July 2024

Manuscript Doi: 10.1093/ecco-jcc/jjae089

Figure 2. Treatment algorithm for Class 2A CD fistulae aiming for repair.



Accepted Manuscript

Downloaded from https://academic.oup.com/ecco-jcc/advance-article/doi/10.1093/ecco-jcc/jjae089/7693896 by KU Leuven Libraries user on 04 July 2024