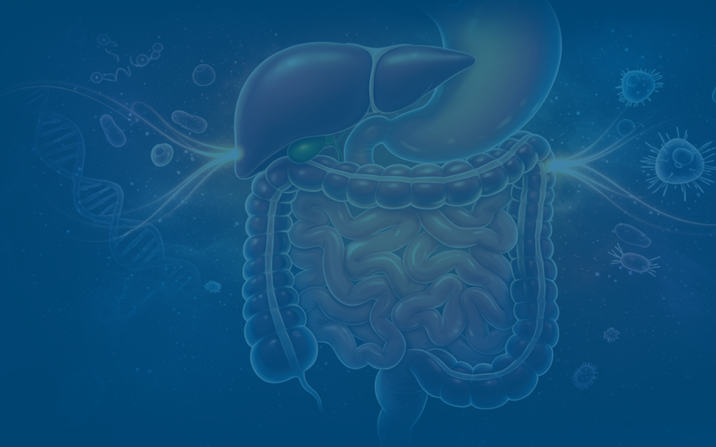




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GİRİŞ

Crohn hastalığı bağırsak katmanlarının tamamını tutabilen kronik inflamatuvar bir hastalık olarak tanımlanır. Sıklıkla ileoçekal bölgeyi tutar, sadece kolonu ya da incebağırsığı da etkileyebilir. Nadiren gastrointestinal traktusun bağırsak dışı bir alanında ortaya çıkar. Crohn hastalığı her yaşta tanı alabilir. Crohn hastalığının iki ana komplikasyonu darlık ve fistül oluşturmalarıdır. Fistüller ince bağırsak ve kolon arasında ya da ince bağırsak anslarının kendi aralarında gelişebilir, mesane ya da vajina gibi diğer organlara veya cilt yoluyla dış ortama açılabilirler. Luminal darlık kronik inflamasyonunun geliştirdiği fibrozun sıklıkla ileoçekal valv bölgesinde daralmaya yol açmasıyla ortaya çıkar, ancak kolonda ve proksimal ince bağırsakta da görülebilirler. Crohn hastalığının endoskopik olarak atlamalı tutulum oluşturmaları, kenarları düzensiz ya da çekintili ülserler ya da uzun aksa paralel ülserler oluşturmaları tipik bulgular olarak kabul edilirler. Perianal fistül Crohn hastalığının en zor tedavi edilen bulgularındandır, hayat kalitesine üzerindeki olumsuz etkisi çok belirgindir, refrakter vakalarda kalıcı ostomi gerektirecek kadar ciddi bir tutulumdur. Crohn hastalığında medikal tedavinin felsefesi hastalığın erken döneminde yeterli

etkinlikte bir tedavi yaparak hastalığın transmural komplikasyonlarının yani fistülizan ve stenoizan hastalığın gelişmesini engellemektir. Bunun için ana hedef mukozal remisyondur. Ancak gerçekte ulaşılması gereken hedef mukozanın yanında tüm bağırsak katlarının ve mezenter inflamasyonunun da iyileşmesidir. Günümüzdeki tedavi seçenekleri ile çoğu hastada bu hedefe ulaşmak mümkün olmamaktadır. Bu nedenle birçok hastada uzun süreli veya ömür boyu süren medikal tedavi gerekeceği kabul edilmelidir. Tedavinin süresinin ve şeklinin hastalık süresi, hastanın yaşı, cinsi, tutulum alanı, hastalığın doğal seyri, komplikasyonları ve sigara gibi çok sayıda faktörle ilişkili olarak şekillendirileceği söylenebilir. Belki de en önemlisi hastanın tedavi edilme konudaki isteği ve sizinle iş birliği yapma kabiliyetidir.

CROHN HASTALIĞI PATOGENEZİ

Crohn hastalığının etyolojisi bir önceki bölümde anlatıldığından bu bölüme patogenezi ile başlamıştır.

Patogenezi konusundaki bilginiz kısıtlıdır. İBH'nın neden ve nasıl ortaya çıktığı halen tam olarak bilinmemektedir. İnflamatuvar bağırsak

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KAYNAKLAR

- Noble AJ, Nowak JK, Adams AT, et al. Defining Interactions Between the Genome, Epigenome, and the Environment in Inflammatory Bowel Disease: Progress and Prospects. *Gastroenterology*. 2023;165(1):44-60.e2. doi:10.1053/j.gastro.2023.03.238
- Rogler G, Biedermann L, Scharl M. New insights into the pathophysiology of inflammatory bowel disease: microbiota, epigenetics and common signalling pathways. *Swiss Med Wkly*. 2018;148:w14599. Published 2018 Mar 22. doi:10.4414/smww.2018.14599
- Cho JH, Brant SR. Recent insights into the genetics of inflammatory bowel disease. *Gastroenterology*. 2011 May;140(6):1704-12. doi: 10.1053/j.gastro.2011.02.046. PMID: 21530736; PMCID: PMC4947143.
- Kofla-Dhubacz A, Pytrus T, Akutko K, et al. Etiology of IBD-Is It Still a Mystery? *Int J Mol Sci*. 2022 Oct 18;23(20):12445. doi: 10.3390/ijms232012445. PMID: 36293300; PMCID: PMC9604112.
- Diez-Martin E, Hernandez-Suarez L, Muñoz-Villafranca C, et al. *Inflammatory Bowel Disease: A Comprehensive Analysis of Molecular Bases, Predictive Biomarkers, Diagnostic Methods, and Therapeutic Options*. *Int J Mol Sci*. 2024 Jun 27;25(13):7062. doi: 10.3390/ijms25137062. PMID: 39000169; PMCID: PMC11241012.
- Lee SH, Kwon JE, Cho ML. Immunological pathogenesis of inflammatory bowel disease. *Intest Res*. 2018 Jan;16(1):26-42. doi: 10.5217/ir.2018.16.1.26. Epub 2018 Jan 18. PMID: 29422795; PMCID: PMC5797268.
- Satsangi J, Silverberg MS, Vermeire S, et al. The Montreal classification of inflammatory bowel disease: controversies, consensus, and implications. *Gut*. 2006 Jun;55(6):749-53. doi: 10.1136/gut.2005.082909. PMID: 16698746; PMCID: PMC1856208.
- Louis E, Collard A, Oger AF, et al. Behaviour of Crohn's disease according to the Vienna classification: changing pattern over the course of the disease. *Gut*. 2001 Dec;49(6):777-82. doi: 10.1136/gut.49.6.777. PMID: 11709511; PMCID: PMC1728556.
- Louis E, Michel V, Hugot JP, et al. Early development of stricturing or penetrating pattern in Crohn's disease is influenced by disease location, number of flares, and smoking but not by NOD2/CARD15 genotype. *Gut*. 2003 Apr;52(4):552-7. doi: 10.1136/gut.52.4.552. PMID: 12631668; PMCID: PMC1773596.
- Kobayashi K, Ueno F, Bito S, et al. Development of consensus statements for the diagnosis and management of intestinal Behçet's disease using a modified Delphi approach. *J Gastroenterol*. 2007;42:737-45
- Li J, Li P, Bai J, et al. Discriminating potential of extraintestinal systemic manifestations and colonoscopic features in Chinese patients with intestinal Behçet's disease and Crohn's disease. *Chin Med J (Engl)*. 2015;128(2):233-238. doi:10.4103/0366-6999.149213
- Y. Erzin, S.N. Esatoglu, I. Hatemi, et al. P259 Comparative retrospective assessment of prospectively recorded endoscopic and histological findings between CD and GI-TB; the first Eastern European registry data, *Journal of Crohn's and Colitis*, Volume 8, Issue Supplement_1, February 2014, Page S171, [https://doi.org/10.1016/S1873-9946\(14\)60380-9](https://doi.org/10.1016/S1873-9946(14)60380-9)
- Tandon HD, Prakash A. Pathology of intestinal tuberculosis and its distinction from Crohn's disease. *Gut*. 1972;13(4):260-269.
- Lichtenstein GR, Loftus EV, Isaacs KL, et al. ACG clinical guideline: management of Crohn's disease in adults [published correction appears in *Am J Gastroenterol*. 2018; 113(7): 1101]. *Am J Gastroenterol*. 2018; 113(4): 481-517.
- Voudoukis E, Karmiris K, Oustamanolakis P, et al. Association between thrombocytosis and iron deficiency anemia in inflammatory bowel disease. *Eur J Gastroenterol Hepatol* 2013;25: 1212 - 6.
- Magro F, Sousa P, Ministro P. C-reactive protein in Crohn's disease: how informative is it? *Expert Rev Gastroenterol Hepatol*. 2014; 8: 392 - 408
- Menees S, Powell C, Kurlander J et al. A meta-analysis of the utility of C-reactive protein, erythrocyte sedimentation rate, fecal calprotectin, and fecal lactoferrin to exclude inflammatory bowel disease in adults with IBS. *Am J Gastroenterol* 2015; 110: 444 - 54.
- Dai C, Jiang M, Sun MJ. The utility of C-reactive protein, erythrocyte sedimentation rate, fecal calprotectin and fecal lactoferrin to exclude inflammatory bowel disease in adults with IBS. *Am J Gastroenterol*. 2015;110(8):1242-1243. doi:10.1038/ajg.2015.194
- Kennedy NA, Clark A, Walkden A. et al. Clinical utility and diagnostic accuracy of faecal calprotectin for IBD at first presentation to gastroenterology services in adults aged 16-50 years. *J Crohns Colitis* 2015; 9: 41 - 9.
- Gisbert JP, Bermejo F, Perez-Calle JL, et al. Fecal calprotectin and lactoferrin for the prediction of inflammatory bowel disease relapse. *Inflamm Bowel Dis* 2009; 15:1190-8.
- Vinding KK, Elsberg H, Thorkilgaard T. et al. Fecal calprotectin measured by patients at home using smartphones—a new clinical tool in monitoring patients with inflammatory bowel disease. *Inflamm Bowel Dis* 2016; 22:336-44.
- Waugh N, Cummins E, Royle P, et al. Faecal calprotectin testing for differentiating amongst inflammatory and non-inflammatory bowel diseases: systematic review and economic evaluation. *Health Technol Assess*. 2013; 17(55): xv-xix, 1-211.
- Van Rheeën PF, Van de Vijver E, Fidler V. Faecal calprotectin for screening of patients with suspected inflammatory bowel disease: diagnostic meta-analysis. *BMJ* 2010; 341: c3369
- Lozoya Angulo ME, de Las Heras Gomez I, Martinez Villanueva M. et al. Faecal calprotectin, a useful marker in discriminating between inflammatory bowel disease and functional gastrointestinal disorders. *Gastroenterol Hepatol* 2017; 40:125-31.
- Liu J, van Sommeren S, Huang H. et al. Association analyses identify 38 susceptibility loci for inflammatory bowel disease and highlight shared genetic risk across populations. *Nat Genet* 2015; 47: 979 - 86.
- Lee H, Oh H, Yang S et al. X chromosome-wide association study identifies a susceptibility locus for inflammatory bowel disease in Koreans. *J Crohns Colitis* 2017; 11: 820 - 30
- Tsianos E, Katsanos K, Tsianos V. Role of genetics in the

- diagnosis and prognosis of Crohn's disease. *World J Gastroenterol* 2012; 18: 105 – 18.
28. Dubinsky MC, Kugathasan S, Kwon S et al. multi-dimensional prognostic risk assessment identifies association between IL12B variation and surgery in Crohn's disease. *Inflamm Bowel Dis* 2013; 19: 1662 – 70.
 29. Bossuyt X. Serologic markers in inflammatory bowel disease. *Clin Chem* 2006; 52:171-81.
 30. Dubinsky MC, Kugathasan S, Mei L, et al. Western Regional Pediatric IBD Research Alliance; Pediatric IBD Collaborative Research Group; Wisconsin Pediatric IBD Alliance. Increased immune reactivity predicts aggressive complicating Crohn's disease in children. *Clin Gastroenterol Hepatol* 2008; 6:1105–11.
 31. Christian Maaser, Andreas Sturm, Stephan R Vavricka. et al. ECCO-ESGAR Guideline for Diagnostic Assessment in IBD Part 1: Initial diagnosis, monitoring of known IBD, detection of complications, *Journal of Crohn's and Colitis*, Volume 13, Issue 2, February 2019, Pages 144–164K, <https://doi.org/10.1093/ecco-jcc/jjy113>
 32. Geboes K, Ectors N, D'Haens G et al. Is ileoscopy with biopsy worthwhile in patients presenting with symptoms of inflammatory bowel disease. *Am J Gastroenterol* 1998; 93 : 201 – 6.
 33. Daperno M, D'Haens G, Van Assche G et al. Development and validation of a new, simplified endoscopic activity score for Crohn's disease: the SES-CD. *Gastrointest Endosc* 2004; 60 : 505 – 12.
 34. Rutgeerts P, Onette E, Vantrappen G. et al. Crohn's disease of the stomach and duodenum: a clinical study with emphasis on the value of endoscopy and endoscopic biopsies. *Endoscopy* 1980; 12: 288 – 94.
 35. Annunziata M, Caviglia R, Papparella L et al. Upper gastrointestinal involvement of Crohn's disease: a prospective study on the role of upper endoscopy in the diagnostic work-up. *Dig Dis Sci* 2012; 57: 1618 – 23.
 36. Mary JY, Modigliani R. Development and validation of an endoscopic index of the severity for Crohn's disease: a prospective multicentre study. Groupe d'Etudes Therapeutiques des Affections Inflammatoires du Tub Digestif [GETAID]. *Gut* 1989; 30:983–9.
 37. Rutgeerts P, Geboes K, Vantrappen G. et al. Predictability of the postoperative course of Crohn's disease. *Gastroenterology* 1990; 99:956–63.
 38. Hamilton AL, De Cruz P, Wright EK. et al. Non-invasive Serological Monitoring for Crohn's Disease Postoperative Recurrence. *J Crohns Colitis*. 2022;16(12):1797-1807. doi:10.1093/ecco-jcc/jjac076
 39. Sands BE. From symptom to diagnosis: clinical distinctions among various forms of intestinal inflammation. *Gastroenterology* 2004; 126:1518.
 40. Surawicz CM, Haggitt RC, Husseman M. et al. Mucosal biopsy diagnosis of colitis: acute self-limited colitis and idiopathic inflammatory bowel disease. *Gastroenterology* 1994; 107:755.
 41. Gomollón F, Dignass A, Annese V, et al. 3rd European evidence-based consensus on the diagnosis and management of Crohn's disease 2016: part 1: diagnosis and medical management. *J Crohns Colitis*. 2017; 11(1): 3-25.
 42. Panés J, Bouzas R, Chaparro M, et al. Systematic review: the use of ultra-sonography, computed tomography and magnetic resonance imaging for the diagnosis, assessment of activity and abdominal complications of Crohn's disease. *Aliment Pharmacol Ther*. 2011; 34(2): 125-145.
 43. Adler J, Punglia D, Dillman J et al. Computed tomography enterography findings correlate with tissue inflammation, not fibrosis in resected small bowel Crohn's disease. *Inflamm Bowel Dis* 2012; 18: 849 – 56.
 44. Novak KL, Nylund K, Maaser C, et al. Expert Consensus on Optimal Acquisition and Development of the International Bowel Ultrasound Segmental Activity Score [IBUS-SAS]: A Reliability and Inter-rater Variability Study on Intestinal Ultrasonography in Crohn's Disease. *J Crohns Colitis*. 2021;15(4):609–16. <https://doi.org/10.1093/ecco-jcc/jjaa216>.
 45. Calabrese E, Kucharzik T, Maaser C, et al. Real-time Interobserver Agreement in Bowel Ultrasonography for Diagnostic Assessment in Patients with Crohn's Disease: An International Multicenter Study. *Inflamm Bowel Dis*. 2018;24(9):2001–6. <https://doi.org/10.1093/ibd/izy091>
 46. Pallotta N, Vincoli G, Montesani C, et al. Small intestine contrast ultrasonography [SICUS] for the detection of small bowel complications in Crohn's disease: a prospective comparative study versus intraoperative findings. *Inflamm Bowel Dis* 2012; 18:74–84.
 47. Kucharzik T, Maaser C. Intestinal ultrasound and management of small bowel Crohn's disease. *Therap Adv Gastroenterol*. 2018; 11:1756284818771367. <https://doi.org/10.1177/1756284818771367>.
 48. 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(2):144–64. <https://doi.org/10.1093/ecco-jcc/jjy113>.
 49. Ahmed O, Rodrigues DM, Nguyen GC. Magnetic resonance imaging of the small bowel in Crohn's disease: a systematic review and meta-analysis. *Can J Gastroenterol Hepatol* 2016; 2016:7857352.
 50. Dionisio P, Gurudu S, Leighton J et al. Capsule endoscopy has a significantly higher diagnostic yield in patients with suspected and established small-bowel Crohn's disease: a meta-analysis. *Am J Gastroenterol* 2010; 105: 1240 – 8.
 51. Cheon JH, Kim YS, Lee IS, et al.; Korean Gut Image Study Group. Can we predict spontaneous capsule passage after retention? A nationwide study to evaluate the incidence and clinical outcomes of capsule retention. *Endoscopy* 2007; 39:1046–52.
 52. Dozsa C, Malbaski N, Borcsek B. Cost-effectiveness analysis of capsule endoscopy using for diagnosing small bowel Crohn's disease. *Value Health* 2015;18: A355.
 53. Jang HJ, Choi MH, Eun CS. et al. Clinical usefulness of double balloon enteroscopy in suspected Crohn's disease: the KASID multi-center trial. *Hepatogastroenterology* 2014; 61:1292–6.
 54. Colombel JF, Solem CA, Sandborn WJ. et al. Quantitative measurement and visual assessment of ileal Crohn's disease activity by computed tomography enterography: correlation with endoscopic severity and C reactive protein. *Gut* 2006; 55:1561–7.
 55. Lee SS, Kim AY, Yang SK, et al. Crohn disease of the small bowel: comparison of CT enterography, MR enterography, and small bowel followthrough as diagnostic tech-

- niques. *Radiology* 2009; 251:751–61.
56. Gecse KB, Brandse JF, van Wilpe S. et al. Impact of disease location on fecal calprotectin levels in Crohn's disease. *Scand J Gastroenterol*. 2015 Jul;50(7):841-7. doi: 10.3109/00365521.2015.1008035. Epub 2015 Jan 30. PMID: 25636819.
 57. Ananthakrishnan AN, Adler J, Chachu KA. et al. AGA Clinical Practice Guideline on the Role of Biomarkers for the Management of Crohn's Disease. *Gastroenterology*. 2023 Dec;165(6):1367-1399. doi: 10.1053/j.gastro.2023.09.029. PMID: 37981354.
 58. Cosnes J, Bourrier A, Nion-Larmurier I. et al. Factors affecting outcomes in Crohn's disease over 15 years. *Gut*. 2012 Aug;61(8):1140-5. doi: 10.1136/gut.jnl-2011-301971. Epub 2012 Mar 2. PMID: 22387526; PMCID: PMC3388724.
 59. Lee S, Kuenzig ME, Ricciuto A. et al. Smoking May Reduce the Effectiveness of Anti-TNF Therapies to Induce Clinical Response and Remission in Crohn's Disease: A Systematic Review and Meta-analysis. *J Crohns Colitis*. 2021 Jan 13;15(1):74-87. doi: 10.1093/ecco-jcc/jjaa139. PMID: 32621742.
 60. Bak MTJ, Demers K, Hammoudi N. et al. Systematic review: Patient-related, microbial, surgical, and histopathological risk factors for endoscopic post-operative recurrence in patients with Crohn's disease. *Aliment Pharmacol Ther*. 2024 Aug;60(3):310-326. doi: 10.1111/apt.18040. Epub 2024 Jun 17. PMID: 38887827.
 61. Burisch J, Kiudelis G, Kupcinskas L. et al. Natural disease course of Crohn's disease during the first 5 years after diagnosis in a European population-based inception cohort: an Epi-IBD study. *Gut*. 2019 Mar;68(3):423-433. doi: 10.1136/gutjnl-2017-315568. Epub 2018 Jan 23. PMID: 29363534.
 62. Noor NM, Lee JC, Bond S. et al. PROFILE Study Group. A biomarker-stratified comparison of top-down versus accelerated step-up treatment strategies for patients with newly diagnosed Crohn's disease (PROFILE): a multicentre, open-label randomised controlled trial. *Lancet Gastroenterol Hepatol*. 2024 May;9(5):415-427. doi: 10.1016/S2468-1253(24)00034-7. Epub 2024 Feb 22. PMID: 38402895; PMCID: PMC11001594.
 63. Fernandes SR, Bernardo S, Saraiva S. et al. The degree of bowel remission predicts phenotype progression in Crohn's disease. *United European Gastroenterol J*. 2024 Sep;12(7):891-900. doi: 10.1002/ueg2.12581. Epub 2024 May 16. PMID: 38753521; PMCID: PMC11497657.
 64. Kim JW, Lee HS, Ye BD. et al. Incidence of and Risk Factors for Free Bowel Perforation in Patients with Crohn's Disease. *Dig Dis Sci*. 2017 Jun;62(6):1607-1614. doi: 10.1007/s10620-017-4539-5. Epub 2017 Mar 17. PMID: 28315037.
 65. Adamina M, Minozzi S, Warusavitarne J. et al. ECCO Guidelines on Therapeutics in Crohn's Disease: Surgical Treatment. *J Crohns Colitis*. 2024 Oct 15;18(10):1556-1582. doi: 10.1093/ecco-jcc/jjae089. PMID: 38878002.
 66. Kelm M, Benatzky C, Buck V. et al. Positive resection margins in Crohn's disease are a relevant risk factor for postoperative disease recurrence. *Sci Rep*. 2024 May 11;14(1):10823. doi: 10.1038/s41598-024-61697-w. PMID: 38734721; PMCID: PMC11088694.
 67. Shah RS, Bachour S, Joseph A. et al. Real-World Surgical and Endoscopic Recurrence Based on Risk Profiles and Prophylaxis Utilization in Postoperative Crohn's Disease. *Clin Gastroenterol Hepatol*. 2024 Apr;22(4):847-857.e12. doi: 10.1016/j.cgh.2023.10.009. Epub 2023 Oct 23. PMID: 37879523.
 68. De Cruz P, Hamilton AL, Burrell KJ. et al. Endoscopic Prediction of Crohn's Disease Postoperative Recurrence. *Inflamm Bowel Dis*. 2022 May 4;28(5):680-688. doi: 10.1093/ibd/izab134. PMID: 34231852.
 69. Rivière P, Vermeire S, Irles-Depe M. et al. No change in determining Crohn's disease recurrence or need for endoscopic or surgical intervention with modification of the Rutgeerts' scoring system. *Clin Gastroenterol Hepatol*. 2019; 17:1643–1645
 70. Regueiro M, Feagan BG, Zou B. et al. PREVENT Study Group. Infliximab Reduces Endoscopic, but Not Clinical, Recurrence of Crohn's Disease After Ileocolonic Resection. *Gastroenterology*. 2016 Jun;150(7):1568-1578. doi: 10.1053/j.gastro.2016.02.072. Epub 2016 Mar 3. PMID: 26946343.
 71. Frieri G, Valvano M, Frassino S. et al. Prophylactic Treatment with Vedolizumab in the Prevention of Post-operative Recurrence (POR) in High-Risk Crohn's Patients. *J Clin Med*. 2023 Apr 26;12(9):3130. doi: 10.3390/jcm12093130. PMID: 37176570; PMCID: PMC10179568.
 72. Tsai L, McCurdy JD, Ma C. et al. Epidemiology and Natural History of Perianal Crohn's Disease: A Systematic Review and Meta-Analysis of Population-Based Cohorts. *Inflamm Bowel Dis*. 2022 Oct 3;28(10):1477-1484. doi: 10.1093/ibd/izab287. PMID: 34792604; PMCID: PMC9527611.
 73. arian AM, Obi M, Fleshner P, Schwartz DA. Management of Perianal Crohn's Disease. *Am J Gastroenterol*. 2023;118(8):1323-1331. doi:10.14309/ajg.0000000000002326
 74. Sandborn WJ, Fazio VW, Feagan BG. et al. American Gastroenterological Association Clinical Practice Committee. AGA technical review on perianal Crohn's disease. *Gastroenterology*. 2003;125(5):1508-1530. doi: 10.1016/j.gastro.2003.08.025
 75. West RL, van der Woude CJ, Hansen BE. et al. Clinical and endosonographic effect of ciprofloxacin on the treatment of perianal fistulae in Crohn's disease with infliximab: a double-blind placebo-controlled study. *Aliment Pharmacol Ther*. 2004 Dec;20(11-12):1329-36. doi: 10.1111/j.1365-2036.2004.02247.x. PMID: 15606395.
 76. 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 Feb;63(2):292-9. doi: 10.1136/gut.jnl-2013-304488. Epub 2013 Mar 23. PMID: 23525574.
 77. 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 May 6;340(18):1398-405. doi: 10.1056/NEJM199905063401804. PMID: 10228190.
 78. Sands BE, Anderson FH, Bernstein CN. et al. Infliximab maintenance therapy for fistulizing Crohn's disease. *N Engl J Med*. 2004 Feb 26;350(9):876-85. doi: 10.1056/NEJMoa030815. PMID: 14985485.

79. Strik AS, Löwenberg 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 Apr;54(4):453-458. doi: 10.1080/00365521.2019.1600014.
80. 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 Apr;45(7):933-940. doi: 10.1111/apt.13970.
81. Gordon H, Minozzi S, Kopylov U, et al. ECCO Guidelines on Therapeutics in Crohn's Disease: Medical Treatment. *J Crohns Colitis*. 2024 Oct 15;18(10):1531-1555. doi: 10.1093/ecco-jcc/jjae091. PMID: 38877997.
82. 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*. 2024 Mar 1;18(3):375-391. doi: 10.1093/ecco-jcc/jjad159.
83. Zeng Z, Lin H, Jiang M, et al. Anti-TNF α in inflammatory bowel disease: from originators to biosimilars. *Front Pharmacol*. 2024 Jul 24; 15:1424606. doi: 10.3389/fphar.2024.1424606. PMID: 39114362; PMCID: PMC11303209.
84. Chupin A, Perduca V, Meyer A, et al. Systematic review with meta-analysis: comparative risk of lymphoma with anti-tumour necrosis factor agents and/or thiopurines in patients with inflammatory bowel disease. *Aliment Pharmacol Ther*. 2020 Oct;52(8):1289-1297. doi: 10.1111/apt.16050.
85. Patel V, Wang Y, MacDonald JK, McDonald JW, Chande N. Methotrexate for maintenance of remission in Crohn's disease. *Cochrane Database Syst Rev*. 2014;2014(8):CD006884. Published 2014 Aug 26. doi: 10.1002/14651858.CD006884.pub3
86. Hanauer SB, Feagan BG, Lichtenstein GR, et al. Maintenance infliximab for Crohn's disease: the ACCENT I randomised trial. *Lancet*. 2002;359(9317):1541-1549. doi:10.1016/S0140-6736(02)08512-4
87. Sands BE, Anderson FH, Bernstein CN, et al. Infliximab maintenance therapy for fistulizing Crohn's disease. *N Engl J Med*. 2004 Feb 26;350(9):876-85. doi: 10.1056/NEJMoa030815. PMID: 14985485.
88. Rutgeerts P, Sandborn WJ, Feagan BG, et al. Infliximab for induction and maintenance therapy for ulcerative colitis [published correction appears in *N Engl J Med*. 2006 May 18;354(20):2200]. *N Engl J Med*. 2005;353(23):2462-2476. doi:10.1056/NEJMoa050516
89. Laharie D, Bourreille A, Branche J, et al. Evolution of Endoscopic Lesions in Steroid-Refractory Acute Severe Ulcerative Colitis Responding to Infliximab or Cyclosporine. *Clin Gastroenterol Hepatol*. 2021;19(6):1180-1188. e4. doi: 10.1016/j.cgh.2020.
90. Hanauer SB, Sandborn WJ, Rutgeerts P, et al. Human anti-tumor necrosis factor monoclonal antibody (adalimumab) in Crohn's disease: the CLASSIC-I trial. *Gastroenterology*. 2006;130(2):323-591. doi: 10.1053/j.gastro.2005.11.030
91. Sandborn WJ, Hanauer SB, Rutgeerts P, et al. Adalimumab for maintenance treatment of Crohn's disease: results of the CLASSIC II trial. *Gut*. 2007;56(9):1232-1239. doi:10.1136/gut.2006.106781
92. Reinisch W, Sandborn WJ, Hommes DW, et al. Adalimumab for induction of clinical remission in moderately to severely active ulcerative colitis: results of a randomised controlled trial. *Gut*. 2011;60(6):780-787. doi:10.1136/gut.2010.221127
93. Sandborn WJ, van Assche G, Reinisch W, et al. Adalimumab induces and maintains clinical remission in patients with moderate-to-severe ulcerative colitis. *Gastroenterology*. 2012;142(2):257-65. e653. doi: 10.1053/j.gastro.2011.10.032
94. Sandborn WJ, Feagan BG, Marano C, et al. Subcutaneous golimumab induces clinical response and remission in patients with moderate-to-severe ulcerative colitis. *Gastroenterology*. 2014;146(1):85-e15. doi: 10.1053/j.gastro.2013.05.048
95. Sandborn WJ, Feagan BG, Marano C, et al. Subcutaneous golimumab maintains clinical response in patients with moderate-to-severe ulcerative colitis. *Gastroenterology*. 2014;146(1):96-109.e1. doi: 10.1053/j.gastro.2013.06.010
96. Schreiber S, Khaliq-Kareemi M, Lawrance IC, et al. Maintenance therapy with certolizumab pegol for Crohn's disease. *N Engl J Med*. 2007;357(3):239-50.
97. Manceño Marcos N, Novella Arribas B, Mora Navarro G, et al. Efficacy and safety of proactive drug monitoring in inflammatory bowel disease treated with anti-TNF agents: A systematic review and meta-analysis. *Dig Liver Dis*. 2024 Mar;56(3):421-428. doi: 10.1016/j.dld.2023.06.028.
98. Sethi S, Dias S, Kumar A, et al. The efficacy of therapeutic drug monitoring of anti-TNF-therapy in inflammatory bowel disease. *Aliment Pharmacol Ther*. 2023 Jun;57(12):1362-1374. doi: 10.1111/apt.17313.
99. Lowell JA, Sharma G, Chua V, et al. Reactive Immunosuppression Addition to Infliximab Monotherapy Restores Clinical Response in Inflammatory Bowel Disease: A Meta-Analysis. *Dig Dis Sci*. 2024 Oct;69(10):3920-3931. doi: 10.1007/s10620-024-08515-5.
100. Lemaitre M, Kirchgessner J, Rudnicki A, et al. Association Between Use of Thiopurines or Tumor Necrosis Factor Antagonists Alone or in Combination and Risk of Lymphoma in Patients with Inflammatory Bowel Disease. *JAMA*. 2017 Nov 7;318(17):1679-1686. doi: 10.1001/jama.2017.16071.
101. Chupin A, Perduca V, Meyer A, et al. Systematic review with meta-analysis: comparative risk of lymphoma with anti-tumour necrosis factor agents and/or thiopurines in patients with inflammatory bowel disease. *Aliment Pharmacol Ther*. 2020 Oct;52(8):1289-1297. doi: 10.1111/apt.16050.
102. Parakkal D, Sifuentes H, Semer R, et al. Hepatosplenic T-cell lymphoma in patients receiving TNF- α inhibitor therapy: expanding the groups at risk. *Eur J Gastroenterol Hepatol*. 2011 Nov;23(12):1150-6. doi: 10.1097/MEG.0b013e32834bb90a.
103. Esse S, Mason KJ, Green AC, et al. Melanoma Risk in Patients Treated with Biologic Therapy for Common Inflammatory Diseases: A Systematic Review and Meta-analysis. *JAMA Dermatol*. 2020 Jul 1;156(7):787-794. doi: 10.1001/jamadermatol.2020.1300.
104. Mariette X, Matucci-Cerinic M, Pavelka K, et al. Malignancies associated with tumour necrosis factor inhibitors in registries and prospective observational studies: a sys-

- tematic review and meta-analysis. *Ann Rheum Dis* 2011; 70:1895.
105. Muller M, D'Amico F, Bonovas S, et al. TNF Inhibitors and Risk of Malignancy in Patients with Inflammatory Bowel Diseases: A Systematic Review. *J Crohns Colitis*. 2021 May 4;15(5):840-859. doi: 10.1093/ecco-jcc/jjaa186.
 106. Nyboe Andersen N, Pasternak B, Basit S, et al. Association between tumor necrosis factor- α antagonists and risk of cancer in patients with inflammatory bowel disease. *JAMA*. 2014;311(23):2406-2413. doi:10.1001/jama.2014.5613
 107. Gupta A, Peyrin-Biroulet L, Ananthakrishnan AN. Risk of Cancer Recurrence in Patients with Immune-Mediated Diseases with Use of Immunosuppressive Therapies: An Updated Systematic Review and Meta-Analysis. *Clin Gastroenterol Hepatol*. 2024;22(3):499-512.e6. doi: 10.1016/j.cgh.2023.07.027
 108. Nguyen GC, Seow CH, Maxwell C, et al. The Toronto Consensus Statements for the Management of Inflammatory Bowel Disease in Pregnancy. *Gastroenterology* 2016; 150:734.
 109. Sandborn WJ, Gasink C, Gao LL, et al.; CERTIFI Study Group. Ustekinumab induction and maintenance therapy in refractory Crohn's disease. *N Engl J Med* 2012; 367:1519-28.
 110. MacDonald JK, Nguyen TM, Khanna R, et al. Anti-IL-12/23p40 antibodies for induction of remission in Crohn's disease. *Cochrane Database Syst Rev*. 2016;11(11):CD007572. Published 2016 Nov 25. doi: 10.1002/14651858.CD007572.pub3
 111. Sandborn WJ, Feagan BG, Fedorak RN, et al. A randomized trial of Ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with moderate-to-severe Crohn's disease. *Gastroenterology*. 2008;135(4):1130-1141. doi: 10.1053/j.gastro.2008.07.014
 112. Rutgeerts P, Gasink C, Chan D, et al. Efficacy of Ustekinumab for inducing endoscopic healing in patients with Crohn's disease. *Gastroenterology* 2018; 155:1045-58.
 113. Torres J, Bonovas S, Doherty G, et al. ECCO Guidelines on Therapeutics in Crohn's Disease: Medical Treatment. *J Crohns Colitis*. 2020;14(1):4-22. doi:10.1093/ecco-jcc/jjz180
 114. Feagan BG, Sandborn WJ, Gasink C, et al.; UNITI-IM-UNITI Study Group. Ustekinumab as induction and maintenance therapy for Crohn's disease. *N Engl J Med* 2016; 375:1946-60
 115. Sandborn WJ, Feagan BG, Rutgeerts P, et al.; GEMINI 2 Study Group. Vedolizumab as induction and maintenance therapy for Crohn's disease. *N Engl J Med* 2013; 369:711-21.
 116. Colombel JF, Sands BE, Rutgeerts P, et al. The safety of vedolizumab for ulcerative colitis and Crohn's disease. *Gut* 2017; 66:839-51.
 117. Kawalec P, Moćko P. An indirect comparison of ustekinumab and vedolizumab in the therapy of TNF-failure Crohn's disease patients. *J Comp Eff Res* 2018; 7:101-11.
 118. 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.
 119. Sandborn WJ, Feagan BG, Loftus EV Jr, et al. Efficacy and Safety of Upadacitinib in a Randomized Trial of Patients with Crohn's Disease. *Gastroenterology*. 2020;158(8):2123-2138.e8. doi: 10.1053/j.gastro.2020.01.047