

Nazmi Gökhan ÜNVER¹ - Öykü TAYFUR YÜREKLİ²

DOI: 10.37609/akya.3785.c267

EPİDEMİYOLOJİ

İnflamatuvar bağırsak hastalıkları (İBH) bağırsağın immün aracılı gerçekleşen ilerleyici bağırsak hasarına neden olabilen ve klinikte alevlenme ve remisyonlarla seyreden kronik yangısal hastalıklardır. Hayat kalitesi üzerine etkisi ve ciddi morbiditelere yola açabilmesi (darlık, kanama, kanser vb) nedeniyle sağlık sistemleri üzerinde ciddi yük oluşturmaktadır. Biyolojik ajanların giderek kullanımının artması da ciddi maliyet artışına neden olmaktadır. Ülseratif kolit (ÜK) ve Crohn hastalığı (CH) iki ana alt tipi olmakla birlikte %10 kadar hastada endoskopik ve görüntüleme yöntemleriyle ayırıcı tanı yapılamaz, bu hastalar “sınıflanmamış kolit” olarak adlandırılır. Tanı konduğu halde ilk 2 yıl içinde de tanı değişikliği olabilmektedir. Çok eski dönemlere kadar tarihi belgelerde kanama ve ishal ile giden bağırsak hastalıkları tanımlanmış olmakla birlikte tıbbi literatürde ÜK ilk olarak 1859’da Sir Samuel Wilks tarafından tanımlanmışken (1) CH 1932’te Burrill Bernard Crohn, Leon Ginzburg ve Gordon Oppenheimer tarafından yazılan bir makalede tanımlanmıştır (2).

İBH en sık Kuzey yarımkürede özellikle de Kuzey Avrupa, Birleşik Krallık, Kuzey Amerika’da görülür. Kuzey-Güney ülkelerindeki görülme

sıklığındaki farklılığın güneş ışığına Kuzey ülkelerinde daha az maruz kalınmasına bağlı olduğu değerlendirilmektedir. Aslında İBH epidemiyolojisi incelendiğinde 3 farklı alandan bahsedilebilir: 1) Batı toplumları 2) yeni sanayileşmiş ülkeler 3) gelişmekte olan ülkeler. Batı toplumlarında hastalığın görülme sıklığındaki artış stabilize olmuşken bu hastalarda mortalite toplum ortalamasından çok farklı olmadığı için ve İBH genellikle genç yaşta tanı aldığı için 2030’da bazı ülkelerde prevalans oranlarının %1’e yükseleceği şeklinde projeksiyonlar yapılmaktadır (3). Bu da Batı ülkelerinde İBH olanların 10 milyonu geçeceği anlamına gelmektedir (4). 2019’da yapılmış olan bir analizde en yüksek prevalans oranları Amerika ve Çin’de rapor edilmiştir (5). Bir Kanada çalışmasında görülme sıklığının 30/ 100 000 olarak sabitleştiği görülmektedir (6). Ancak aynı çalışmada İBH vakalarının yaşanması ve artan ileri yaş İBH tanıları nedeniyle 65 yaş üzeri 85 kişide 1 İBH görüldüğü ve bu oranın 2008’te 1/154 olduğu rapor edilmiştir. Omsted County, Minnesota’da yapılan toplum bazlı çalışmalarda 1965 yılında CH prevalansı 28/100 000 ÜK için 117/100 000 iken 2011’de İBH genel prevalans oranı 533/100000 olarak rapor edilmiştir (4, 7). Yeni Zelanda ve Avustralya’da da sık görülme oranları bildirilmektedir. Ancak Batı ülkelerinde

¹ Uzm. Dr., Sağlık Bilimleri Üniversitesi, Ankara Bilkent Şehir Hastanesi, Gastroenteroloji Kliniği, Gastroenteroloji Yandal Asistanı, nazmi.gokhan.unver@gmail.com, ORCID iD: 0000-0002-9018-6210

² Doç. Dr., Ankara Yıldırım Beyazıt Üniversitesi, İç Hastalıkları AD., Gastroenteroloji BD., oykutayfur78@yahoo.com, ORCID iD: 000-0002-1295-152X

KAYNAKLAR

- Wilks S. Morbid appearances in the intestine of Miss Bankes. *Med Times Gazette*. 1859;2(2):264-5.
- Crohn BB, Ginzburg L, Oppenheimer GD. Regional ileitis: a pathologic and clinical entity. *Jama*. 1984;251(1):73-9.
- Coward S, Clement F, Benchimol EI, et al. Past and future burden of inflammatory bowel diseases based on modeling of population-based data. *Gastroenterology*. 2019;156(5):1345-53. e4.
- Kaplan GG, Windsor JW. The four epidemiological stages in the global evolution of inflammatory bowel disease. *Nature reviews Gastroenterology & hepatology*. 2021;18(1):56-66.
- Wang R, Li Z, Liu S, et al. Global, regional and national burden of inflammatory bowel disease in 204 countries and territories from 1990 to 2019: a systematic analysis based on the Global Burden of Disease Study 2019. *BMJ open*. 2023;13(3):e065186.
- Coward S, Benchimol EI, Bernstein CN, et al. Forecasting the incidence and prevalence of inflammatory bowel disease: a Canadian nationwide analysis. *Official journal of the American College of Gastroenterology* | ACG. 2024;119(8):1563-70.
- Loftus Jr EV, Silverstein MD, Sandborn WJ, et al. Crohn's disease in Olmsted County, Minnesota, 1940-1993: incidence, prevalence, and survival. *Gastroenterology*. 1998;114(6):1161-8.
- Ananthakrishnan AN, Kaplan GG, Ng SC. Changing global epidemiology of inflammatory bowel diseases: sustaining health care delivery into the 21st century. *Clinical Gastroenterology and Hepatology*. 2020;18(6):1252-60.
- Carroll MW, Kuenzig ME, Mack DR, et al. The impact of inflammatory bowel disease in Canada 2018: children and adolescents with IBD. *Journal of the Canadian Association of Gastroenterology*. 2019;2(Supplement_1):S49-S67.
- Aniwan S, Santiago P, Loftus Jr EV, et al. The epidemiology of inflammatory bowel disease in Asia and Asian immigrants to Western countries. *United European Gastroenterology Journal*. 2022;10(10):1063-76.
- Ng SC, Tang W, Leong RW, et al. Environmental risk factors in inflammatory bowel disease: a population-based case-control study in Asia-Pacific. *Gut*. 2015;64(7):1063-71.
- Barclay AR, Russell RK, Wilson ML, et al. Systematic review: the role of breastfeeding in the development of pediatric inflammatory bowel disease. *The Journal of pediatrics*. 2009;155(3):421-6.
- Elten M, Benchimol EI, Fell DB, et al. Ambient air pollution and the risk of pediatric-onset inflammatory bowel disease: a population-based cohort study. *Environment international*. 2020;138:105676.
- Elten M, Benchimol EI, Fell DB, et al. Residential greenspace in childhood reduces risk of pediatric inflammatory bowel disease: a population-based cohort study. *Official journal of the American College of Gastroenterology* | ACG. 2021;116(2):347-53.
- Torres J, Hu J, Seki A, et al. Infants born to mothers with IBD present with altered gut microbiome that transfers abnormalities of the adaptive immune system to germ-free mice. *Gut*. 2020;69(1):42-51.
- Agrawal M, Jess T. Implications of the changing epidemiology of inflammatory bowel disease in a changing world. *United European gastroenterology journal*. 2022;10(10):1113-20.
- Frisch M, Pedersen BV, Andersson RE. Appendicitis, mesenteric lymphadenitis, and subsequent risk of ulcerative colitis: cohort studies in Sweden and Denmark. *Bmj*. 2009;338.
- Le Berre C, Honap S, Peyrin-Biroulet L. Ulcerative colitis. *Lancet*. 2023;402(10401):571-84.
- Jeuring SE, van den Heuvel TR, Zeegers MP, et al. Epidemiology and Long-term Outcome of Inflammatory Bowel Disease Diagnosed at Elderly Age-An Increasing Distinct Entity? *Inflamm Bowel Dis*. 2016;22(6):1425-34.
- Magro F, Doherty G, Peyrin-Biroulet L, et al. ECCO Position Paper: Harmonization of the Approach to Ulcerative Colitis Histopathology. *J Crohns Colitis*. 2020;14(11):1503-11.
- Fachal L, Consortium OtiIG. OP11 expanded genome-wide association study of inflammatory bowel disease identifies 174 novel loci and directly implicates new genes in disease susceptibility. *Journal of Crohn's and Colitis*. 2022;16(Supplement_1):i011-i3.
- Feldman M, Friedman LS, Brandt LJ. Sleisenger and Fordtran's gastrointestinal and liver disease E-book: pathophysiology, diagnosis, management: Elsevier health sciences; 2020.
- Kaur A, Goggolidou P. Ulcerative colitis: understanding its cellular pathology could provide insights into novel therapies. *Journal of inflammation*. 2020;17:1-8.
- Uzzan M, Martin JC, Mesin L, et al. Ulcerative colitis is characterized by a plasmablast-skewed humoral response associated with disease activity. *Nature medicine*. 2022;28(4):766-79.
- Haberman Y, Karns R, Dexheimer PJ, et al. Ulcerative colitis mucosal transcriptomes reveal mitochondriopathy and personalized mechanisms underlying disease severity and treatment response. *Nature communications*. 2019;10(1):38.
- Narula N, Wong EC, Dehghan M, et al. Association of ultra-processed food intake with risk of inflammatory bowel disease: prospective cohort study. *Bmj*. 2021;374.
- Racine A, Carbonnel F, Chan SS, et al. Dietary patterns and risk of inflammatory bowel disease in Europe: results from the EPIC study. *Inflammatory bowel diseases*. 2016;22(2):345-54.
- Khan N, Patel D, Shah Y, et al. Albumin as a prognostic marker for ulcerative colitis. *World Journal of Gastroenterology*. 2017;23(45):8008.
- Peyrin-Biroulet L, Panés J, Sandborn WJ, et al. Defining disease severity in inflammatory bowel diseases: current and future directions. *Clinical Gastroenterology and Hepatology*. 2016;14(3):348-54. e17.
- Schroeder KW, Tremaine WJ, Ilstrup DM. Coated oral 5-aminosalicylic acid therapy for mildly to moderately active ulcerative colitis. *New England Journal of Medicine*. 1987;317(26):1625-9.
- Van Rheenen PF, Van de Vijver E, Fidler V. Faecal calprotectin for screening of patients with suspected inflammatory bowel disease: diagnostic meta-analysis. *Bmj*. 2010;341.
- Ricciuto A, Kamath BM, Griffiths AM. The IBD and PSC

- Phenotypes of PSC-IBD. *Current gastroenterology reports*. 2018;20:1-13.
33. Erden A, Öz DK, Çoruh AG, et al. Backwash ileitis in ulcerative colitis: Are there MR enterographic features that distinguish it from Crohn disease? *European Journal of Radiology*. 2019;110:212-8.
34. Eaden J, Abrams K, Mayberry J. The risk of colorectal cancer in ulcerative colitis: a meta-analysis. *Gut*. 2001;48(4):526-35.
35. Gordon H, Biancone L, Fiorino G, et al. ECCO guidelines on inflammatory bowel disease and malignancies. *Journal of Crohn's and Colitis*. 2023;17(6):827-54.
36. Satsangi J, Silverberg M, Vermeire S, et al. The Montreal classification of inflammatory bowel disease: controversies, consensus, and implications. *Gut*. 2006;55(6):749-53.
37. Fumery M, Singh S, Dulai PS, et al. Natural history of adult ulcerative colitis in population-based cohorts: a systematic review. *Clinical Gastroenterology and Hepatology*. 2018;16(3):343-56. e3.
38. Roda G, Narula N, Pinotti R, et al. Systematic review with meta-analysis: proximal disease extension in limited ulcerative colitis. *Alimentary pharmacology & therapeutics*. 2017;45(12):1481-92.
39. Travis SP, Schnell D, Krzeski P, et al. Reliability and initial validation of the ulcerative colitis endoscopic index of severity. *Gastroenterology*. 2013;145(5):987-95.
40. Kawashima K, Oshima N, Kishimoto K, et al. Low fecal calprotectin predicts histological healing in patients with ulcerative colitis with endoscopic remission and leads to prolonged clinical remission. *Inflammatory Bowel Diseases*. 2023;29(3):359-66.
41. D'Amico F, Fiorino G, Solitano V, et al. Ulcerative colitis: Impact of early disease clearance on long-term outcomes-A multicenter cohort study. *United European gastroenterology journal*. 2022;10(7):775-82.
42. Solberg IC, Lygren I, Jahnsen J, et al. Clinical course during the first 10 years of ulcerative colitis: results from a population-based inception cohort (IBSEN Study). *Scandinavian journal of gastroenterology*. 2009;44(4):431-40.
43. Peyrin-Biroulet L, Sandborn W, Sands BE, et al. Selecting therapeutic targets in inflammatory bowel disease (STRIDE): determining therapeutic goals for treat-to-target. *Official journal of the American College of Gastroenterology* | ACG. 2015;110(9):1324-38.
44. Turner D, Ricciuto A, Lewis A, et al. STRIDE-II: an update on the Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE) Initiative of the International Organization for the Study of IBD (IOIBD): determining therapeutic goals for treat-to-target strategies in IBD. *Gastroenterology*. 2021;160(5):1570-83.
45. Frøslie KE, Jahnsen J, Moum BA, et al. Mucosal healing in inflammatory bowel disease: results from a Norwegian population-based cohort. *Gastroenterology*. 2007;133(2):412-22.
46. Colombel JF, Rutgeerts P, Reinisch W, et al. Early mucosal healing with infliximab is associated with improved long-term clinical outcomes in ulcerative colitis. *Gastroenterology*. 2011;141(4):1194-201.
47. Silverberg MS, Satsangi J, Ahmad T, et al. Toward an integrated clinical, molecular and serological classification of inflammatory bowel disease: report of a Working Party of the 2005 Montreal World Congress of Gastroenterology. *Canadian Journal of Gastroenterology and Hepatology*. 2005;19:5A-36A.
48. Feagan BG, MacDonald JK. Oral 5-aminosalicylic acid for induction of remission in ulcerative colitis. *Cochrane database of systematic reviews*. 2012(10).
49. Plume JL, De A, Mutalib M. Assessing the correlation between fecal calprotectin, blood markers and disease activity in pediatric inflammatory bowel disease. *Annals of Gastroenterology*. 2024;37(4):436.
50. Kosinski LR, Brill J, Regueiro M. Making a medical home for IBD patients. *Current gastroenterology reports*. 2017;19:1-7.
51. Khan AA, Piris J, Truelove S. An experiment to determine the active therapeutic moiety of sulphasalazine. *The Lancet*. 1977;310(8044):892-5.
52. Hanauer SB, Sandborn WJ, Dallaire C, et al. Delayed-Release Oral Mesalamine 4.8 g/day (800 mg tablets) Compared with 2.4 g/day (400 mg tablets) for the Treatment of Mildly to Moderately Active Ulcerative Colitis: The ASCEND I Trial. *Canadian Journal of Gastroenterology and Hepatology*. 2007;21(12):827-34.
53. Hanauer SB, Sandborn WJ, Kornbluth A, et al. Delayed-release oral mesalamine at 4.8 g/day (800 mg tablet) for the treatment of moderately active ulcerative colitis: the ASCEND II trial. *Official journal of the American College of Gastroenterology* | ACG. 2005;100(11):2478-85.
54. Lichtenstein G, Ramsey D, Rubin D. Randomised clinical trial: delayed-release oral mesalazine 4.8 g/day vs. 2.4 g/day in endoscopic mucosal healing-ASCEND I and II combined analysis. *Alimentary pharmacology & therapeutics*. 2011;33(6):672-8.
55. Ford AC, Bernstein CN, Khan KJ, et al. Glucocorticosteroid therapy in inflammatory bowel disease: systematic review and meta-analysis. *Official journal of the American College of Gastroenterology* | ACG. 2011;106(4):590-9.
56. Summers RW, Switz DM, Sessions Jr JT, et al. National Cooperative Crohn's Disease Study: results of drug treatment. *Gastroenterology*. 1979;77(4):847-69.
57. Akobeng AK, Zhang D, Gordon M, et al. Oral 5-aminosalicylic acid for maintenance of medically-induced remission in Crohn's disease. *Cochrane database of systematic reviews*. 2016(9).
58. Gjaffer M, O'Brien C, Holdsworth C. Clinical tolerance to three 5-aminosalicylic acid releasing preparations in patients with inflammatory bowel disease intolerant or allergic to sulphasalazine. *Alimentary pharmacology & therapeutics*. 1992;6(1):51-9.
59. Loftus Jr E, Kane S, Bjorkman D. Short-term adverse effects of 5-aminosalicylic acid agents in the treatment of ulcerative colitis. *Alimentary pharmacology & therapeutics*. 2004;19(2):179-89.
60. Ng SW, Mahadevan U. Management of inflammatory bowel disease in pregnancy. *Expert review of clinical immunology*. 2013;9(2):161-74.
61. Marshall J, Irvine E. Rectal aminosalicilate therapy for distal ulcerative colitis: a meta-analysis. *Alimentary pharmacology & therapeutics*. 1995;9(3):293-300.
62. Cohen RD, Woseth DM, Thisted RA, et al. A meta-analysis and overview of the literature on treatment options for left-sided ulcerative colitis and ulcerative proctitis. *Official journal of the American College of Gastroenterology*

- ACG. 2000;95(5):1263-76.
63. Safdi M, DeMicco M, Sninsky C, et al. A Double--Blind Comparison of Oral versus Rectal Mesalamine versus Combination Therapy in the Treatment of Distal Ulcerative Colitis. *American Journal of Gastroenterology (Springer Nature)*. 1997;92(10).
 64. Stuck AE, Minder CE, Frey FJ. Risk of infectious complications in patients taking glucocorticosteroids. *Reviews of infectious diseases*. 1989;11(6):954-63.
 65. Lewis JD, Gelfand JM, Troxel AB, et al. Immunosuppressant medications and mortality in inflammatory bowel disease. *Official journal of the American College of Gastroenterology* | ACG. 2008;103(6):1428-35.
 66. Munkholm P, Langholz E, Davidsen M, et al. Frequency of glucocorticoid resistance and dependency in Crohn's disease. *Gut*. 1994;35(3):360-2.
 67. Dignass A, Eliakim R, Magro F, et al. Second European evidence-based consensus on the diagnosis and management of ulcerative colitis part 1: definitions and diagnosis. *Journal of Crohn's and Colitis*. 2012;6(10):965-90.
 68. Steinhart AH, Ewe K, Griffiths AM, et al. Corticosteroids for maintenance of remission in Crohn's disease. *Cochrane database of systematic reviews*. 1996;2010(1).
 69. Seow CH, Benchimol EI, Griffiths AM, et al. Budesonide for induction of remission in Crohn's disease. *Cochrane database of systematic reviews*. 2008(3).
 70. Sandborn WJ, Travis S, Moro L, et al. Once-daily budesonide MMX® extended-release tablets induce remission in patients with mild to moderate ulcerative colitis: results from the CORE I study. *Gastroenterology*. 2012;143(5):1218-26. e2.
 71. Sherlock ME, MacDonald JK, Griffiths AM, et al. Oral budesonide for induction of remission in ulcerative colitis. *Cochrane database of systematic reviews*. 2015(10).
 72. Watkinson G. Treatment of ulcerative colitis with topical hydrocortisone hemisuccinate sodium. *British medical journal*. 1958;2(5104):1077.
 73. Mulder CJ, Fockens P, Meijer JW, et al. Beclomethasone dipropionate (3mg) versus 5-aminosalicylic acid (2g) versus the combination of both (3mg/2g) as retention enemas in active ulcerative proctitis. *European journal of gastroenterology & hepatology*. 1996;8(6):549-54.
 74. Löfberg R, Thomsen OQ, Langholz E, et al. Budesonide versus prednisolone retention enemas in active distal ulcerative colitis. *Alimentary pharmacology & therapeutics*. 1994;8(6):623-9.
 75. Ansari A, Arenas M, Greenfield S, et al. Prospective evaluation of the pharmacogenetics of azathioprine in the treatment of inflammatory bowel disease. *Alimentary pharmacology & therapeutics*. 2008;28(8):973-83.
 76. WJ S. Lack of effect of intravenous administration on time to respond to azathioprine for steroid-treated Crohn's disease. *Gastroenterology*. 1999;117:527-35.
 77. Kaczmorski S, Doares W, Winfrey S, et al. Gout and transplantation: new treatment option—same old drug interaction. *Transplantation*. 2011;92(3):e13-e4.
 78. Sparrow MP, Hande SA, Friedman S, et al. Effect of allopurinol on clinical outcomes in inflammatory bowel disease nonresponders to azathioprine or 6-mercaptopurine. *Clinical Gastroenterology and Hepatology*. 2007;5(2):209-14.
 79. Khan KJ, Dubinsky MC, Ford AC, et al. Efficacy of immunosuppressive therapy for inflammatory bowel disease: a systematic review and meta-analysis. *Official journal of the American College of Gastroenterology* | ACG. 2011;106(4):630-42.
 80. Hanauer SB, Sandborn WJ, Lichtenstein GR. Evolving considerations for thiopurine therapy for inflammatory bowel diseases—a clinical practice update: commentary. *Gastroenterology*. 2019;156(1):36-42.
 81. Lamb CA, Kennedy NA, Raine T, et al. British Society of Gastroenterology consensus guidelines on the management of inflammatory bowel disease in adults. *Gut*. 2019;68(Suppl 3):s1-s106.
 82. Miyake N, Ando T, Ishiguro K, et al. Azathioprine is essential following cyclosporine for patients with steroid-refractory ulcerative colitis. *World Journal of Gastroenterology: WJG*. 2015;21(1):254.
 83. Panaccione R, Ghosh S, Middleton S, et al. Combination therapy with infliximab and azathioprine is superior to monotherapy with either agent in ulcerative colitis. *Gastroenterology*. 2014;146(2):392-400. e3.
 84. Jones JL, Kaplan GG, Peyrin-Biroulet L, et al. Effects of concomitant immunomodulator therapy on efficacy and safety of anti-tumor necrosis factor therapy for Crohn's disease: a meta-analysis of placebo-controlled trials. *Clinical Gastroenterology and Hepatology*. 2015;13(13):2233-40. e2.
 85. Chande N, Tsoulis DJ, MacDonald JK. Azathioprine or 6-mercaptopurine for induction of remission in Crohn's disease. *Cochrane database of systematic reviews*. 2013(4).
 86. Prefontaine E, Sutherland LR, MacDonald JK, et al. Azathioprine or 6-mercaptopurine for maintenance of remission in Crohn's disease. *Cochrane Database of Systematic Reviews*. 2009(1).
 87. MT O. Association of 6-thioguanine nucleotide levels and inflammatory bowel disease activity: a meta-analysis. *Gastroenterology*. 2006;130:1047-53.
 88. Dassopoulos T, Dubinsky MC, Bentsen JL, et al. Randomised clinical trial: individualised vs. weight-based dosing of azathioprine in Crohn's disease. *Alimentary pharmacology & therapeutics*. 2014;39(2):163-75.
 89. Hoentjen F, Seinen ML, Hanauer SB, et al. Safety and effectiveness of long-term allopurinol-thiopurine maintenance treatment in inflammatory bowel disease. *Inflammatory bowel diseases*. 2013;19(2):363-9.
 90. Chaparro M, Ordás I, Cabré E, et al. Safety of thiopurine therapy in inflammatory bowel disease: long-term follow-up study of 3931 patients. *Inflammatory bowel diseases*. 2013;19(7):1404-10.
 91. Gisbert JB, González-Lama Y, Maté J. Thiopurine-induced liver injury in patients with inflammatory bowel disease: a systematic review. *Official journal of the American College of Gastroenterology* | ACG. 2007;102(7):1518-27.
 92. Gisbert JB, Gomollón F. Thiopurine-induced myelotoxicity in patients with inflammatory bowel disease: a review. *Official journal of the American College of Gastroenterology* | ACG. 2008;103(7):1783-800.
 93. Linton M, Kroeker K, Fedorak D, et al. Prevalence of Epstein-Barr virus in a population of patients with inflammatory bowel disease: a prospective cohort study. *Alimentary pharmacology & therapeutics*. 2013;38(10):1248-54.
 94. Beaugerie L, Brousse N, Bouvier AM, et al. Lymphoproliferative disorders in patients receiving thiopurines for inflammatory bowel disease: a prospective observational

- cohort study. *The Lancet*. 2009;374(9701):1617-25.
95. Peyrin-Biroulet L, Chevaux J-B, Bouvier A-M, et al. Risk of melanoma in patients who receive thiopurines for inflammatory bowel disease is not increased. *Official journal of the American College of Gastroenterology* ACG. 2012;107(9):1443-4.
96. Long MD, Martin CF, Pipkin CA, et al. Risk of melanoma and nonmelanoma skin cancer among patients with inflammatory bowel disease. *Gastroenterology*. 2012;143(2):390-9. e1.
97. Long MD, Herfarth HH, Pipkin CA, et al. Increased risk for non-melanoma skin cancer in patients with inflammatory bowel disease. *Clinical Gastroenterology and Hepatology*. 2010;8(3):268-74.
98. Jess T, Horváth-Puhó E, Fallingborg J, et al. Cancer risk in inflammatory bowel disease according to patient phenotype and treatment: a Danish population-based cohort study. *Official journal of the American College of Gastroenterology* ACG. 2013;108(12):1869-76.
99. Shelton E, Laharie D, Scott FI, et al. Cancer recurrence following immune-suppressive therapies in patients with immune-mediated diseases: a systematic review and meta-analysis. *Gastroenterology*. 2016;151(1):97-109. e4.
100. Lémann M, Mary J-Y, Colombel J-F, et al. A randomized, double-blind, controlled withdrawal trial in Crohn's disease patients in long-term remission on azathioprine. *Gastroenterology*. 2005;128(7):1812-8.
101. Rampton D. Methotrexate in Crohn's disease. *Gut*. 2001;48(6):790-1.
102. Feagan BG, Rochon J, Fedorak RN, et al. Methotrexate for the treatment of Crohn's disease. *New England Journal of Medicine*. 1995;332(5):292-7.
103. Feagan BG, Fedorak RN, Irvine EJ, et al. A comparison of methotrexate with placebo for the maintenance of remission in Crohn's disease. *New England Journal of Medicine*. 2000;342(22):1627-32.
104. Jundt J, Browne B, Fiocco G, et al. A comparison of low dose methotrexate bioavailability: oral solution, oral tablet, subcutaneous and intramuscular dosing. *The Journal of Rheumatology*. 1993;20(11):1845-9.
105. McDonald JW, Wang Y, Tsoulis DJ, et al. Methotrexate for induction of remission in refractory Crohn's disease. *Cochrane database of systematic reviews*. 2014(8).
106. Oren R, Arber N, Odes S, et al. Methotrexate in Chronic Active Ulcerative Colitis: A Double-Blind, Randomized, Israeli Multicenter Trial. *Gastroenterology-Orlando*. 1996;110(5):1416-21.
107. Carbonnel F, Colombel JF, Filippi J, et al. Methotrexate is not superior to placebo for inducing steroid-free remission, but induces steroid-free clinical remission in a larger proportion of patients with ulcerative colitis. *Gastroenterology*. 2016;150(2):380-8. e4.
108. Herfarth H, Barnes EL, Valentine JF, et al. Methotrexate is not superior to placebo in maintaining steroid-free response or remission in ulcerative colitis. *Gastroenterology*. 2018;155(4):1098-108. e9.
109. Feagan BG, McDonald JW, Panaccione R, et al. Methotrexate in combination with infliximab is no more effective than infliximab alone in patients with Crohn's disease. *Gastroenterology*. 2014;146(3):681-8. e1.
110. Colman RJ, Rubin DT. Optimal doses of methotrexate combined with anti-TNF therapy to maintain clinical remission in inflammatory bowel disease. *Journal of Crohn's and Colitis*. 2015;9(4):312-7.
111. Te Helen S, Schiano TD, Kuan SF, et al. Hepatic effects of long-term methotrexate use in the treatment of inflammatory bowel disease. *Official journal of the American College of Gastroenterology* ACG. 2000;95(11):3150-6.
112. Weber-Schoendorfer C, Hoeltzenbein M, Wacker E, et al. No evidence for an increased risk of adverse pregnancy outcome after paternal low-dose methotrexate: an observational cohort study. *Rheumatology*. 2014;53(4):757-63.
113. Eck LK, Jensen TB, Mastrogiannis D, et al. Risk of adverse pregnancy outcome after paternal exposure to methotrexate within 90 days before pregnancy. *Obstetrics & Gynecology*. 2017;129(4):707-14.
114. Lichtiger S, Present DH, Kornbluth A, et al. Cyclosporine in severe ulcerative colitis refractory to steroid therapy. *New England Journal of Medicine*. 1994;330(26):1841-5.
115. Van Assche G, D'haens G, Noman M, et al. Randomized, double-blind comparison of 4 mg/kg versus 2 mg/kg intravenous cyclosporine in severe ulcerative colitis. *Gastroenterology*. 2003;125(4):1025-31.
116. Laharie D, Bourrille A, Branche J, et al. Ciclosporin versus infliximab in patients with severe ulcerative colitis refractory to intravenous steroids: a parallel, open-label randomised controlled trial. *The Lancet*. 2012;380(9857):1909-15.
117. Williams JG, Alam MF, Alrubaiy L, et al. Infliximab versus ciclosporin for steroid-resistant acute severe ulcerative colitis (CONSTRUCT): a mixed methods, open-label, pragmatic randomised trial. *The lancet Gastroenterology & hepatology*. 2016;1(1):15-24.
118. Kobayashi T, Siegmund B, Le Berre C, et al. Ulcerative colitis. *Nat Rev Dis Primers*. 2020;6(1):74.
119. Moskovitz DN, Van Assche G, Maenhout B, et al. Incidence of colectomy during long-term follow-up after cyclosporine-induced remission of severe ulcerative colitis. *Clinical Gastroenterology and Hepatology*. 2006;4(6):760-5.
120. MB S. Adverse events associated with the use of cyclosporine in patients with inflammatory bowel disease. *Am J Gastroenterol*. 2008;103:937-43.
121. Tedesco D, Haragsim L. Cyclosporine: a review. *Journal of transplantation*. 2012;2012(1):230386.
122. Rutgeerts P, Sandborn WJ, Feagan BG, et al. Infliximab for induction and maintenance therapy for ulcerative colitis. *New England Journal of Medicine*. 2005;353(23):2462-76.
123. 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):780-7.
124. 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.
125. Feagan BG, Rutgeerts P, Sands BE, et al. Vedolizumab as induction and maintenance therapy for ulcerative colitis. *New England Journal of Medicine*. 2013;369(8):699-710.
126. Bressler B, Yarur A, Silverberg MS, et al. Vedolizumab and anti-tumour necrosis factor a real-world outcomes in biologic-naïve inflammatory bowel disease patients: results from the EVOLVE study. *Journal of Crohn's and Colitis*. 2021;15(10):1694-706.

127. Sands BE, Sandborn WJ, Panaccione R, et al. Ustekinumab as induction and maintenance therapy for ulcerative colitis. *New England Journal of Medicine*. 2019;381(13):1201-14.
128. Sandborn WJ, Su C, Sands BE, et al. Tofacitinib as induction and maintenance therapy for ulcerative colitis. *New England Journal of Medicine*. 2017;376(18):1723-36.
129. Vermeire S, Danese S, Zhou W, et al. OP23 Efficacy and safety of upadacitinib as induction therapy in patients with moderately to severely active ulcerative colitis: results from phase 3 U-ACCOMPLISH study. *Journal of Crohn's & Colitis*. 2021;15(Suppl 1):S021.
130. Singh S, Murad MH, Fumery M, et al. First-and second-line pharmacotherapies for patients with moderate to severely active ulcerative colitis: an updated network meta-analysis. *Clinical Gastroenterology and Hepatology*. 2020;18(10):2179-91. e6.
131. Burr NE, Gracie DJ, Black CJ, et al. Efficacy of biological therapies and small molecules in moderate to severe ulcerative colitis: systematic review and network meta-analysis. *Gut*. 2022;71(10):1976-87.
132. Bressler B. Is there an optimal sequence of biologic therapies for inflammatory bowel disease? *Therapeutic Advances in Gastroenterology*. 2023;16:17562848231159452.
133. Sands BE, Peyrin-Biroulet L, Loftus Jr EV, et al. Vedolizumab versus adalimumab for moderate-to-severe ulcerative colitis. *New England Journal of Medicine*. 2019;381(13):1215-26.
134. Gros B, Kaplan GG. Ulcerative colitis in adults: A review. *Jama*. 2023;330(10):951-65.
135. Singh S, Ananthakrishnan AN, Nguyen NH, et al. AGA clinical practice guideline on the role of biomarkers for the management of ulcerative colitis. *Gastroenterology*. 2023;164(3):344-72.
136. Narula N, Marshall JK, Colombel J-F, et al. Systematic review and meta-analysis: infliximab or cyclosporine as rescue therapy in patients with severe ulcerative colitis refractory to steroids. *Official journal of the American College of Gastroenterology* | ACG. 2016;111(4):477-91.
137. Sebastian S, Walker GJ, Kennedy NA, et al. Assessment, endoscopy, and treatment in patients with acute severe ulcerative colitis during the COVID-19 pandemic (PROTECT-ASUC): a multicentre, observational, case-control study. *The Lancet Gastroenterology & Hepatology*. 2021;6(4):271-81.
138. Lee H-S, Park SH, Kim S-H, et al. Risk factors and clinical outcomes associated with cytomegalovirus colitis in patients with acute severe ulcerative colitis. *Inflammatory bowel diseases*. 2016;22(4):912-8.
139. Nguyen GC, Kaplan GG, Harris ML, et al. A national survey of the prevalence and impact of Clostridium difficile infection among hospitalized inflammatory bowel disease patients. *Official journal of the American College of Gastroenterology* | ACG. 2008;103(6):1443-50.
140. Ilvemark JF, Wilkens R, Thielsen P, et al. Early intestinal ultrasound predicts intravenous corticosteroid response in hospitalised patients with severe ulcerative colitis. *Journal of Crohn's and Colitis*. 2022;16(11):1725-34.
141. Turner D, Walsh CM, Steinhart AH, et al. Response to corticosteroids in severe ulcerative colitis: a systematic review of the literature and a meta-regression. *Clinical Gastroenterology and Hepatology*. 2007;5(1):103-10.
142. Ben-Horin S, Har-Noy O, Katsanos KH, et al. Corticosteroids and mesalamine versus corticosteroids for acute severe ulcerative colitis: a randomized controlled trial. *Clinical Gastroenterology and Hepatology*. 2022;20(12):2868-75. e1.
143. Travis S, Farrant J, Ricketts C, et al. Predicting outcome in severe ulcerative colitis. *Gut*. 1996;38(6):905-10.
144. Adams A, Gupta V, Mohsen W, et al. Early management of acute severe UC in the biologics era: development and international validation of a prognostic clinical index to predict steroid response. *Gut*. 2023;72(3):433-42.
145. Travis S, Satsangi J, Lémann M. Predicting the need for colectomy in severe ulcerative colitis: a critical appraisal of clinical parameters and currently available biomarkers. BMJ Publishing Group; 2011. p. 3-9.
146. Salameh R, Kirchgesner J, Allez M, et al. Long-term outcome of patients with acute severe ulcerative colitis responding to intravenous steroids. *Alimentary Pharmacology & Therapeutics*. 2020;51(11):1096-104.
147. Sahu P, Kedia S, Vuyyuru SK, et al. Randomised clinical trial: exclusive enteral nutrition versus standard of care for acute severe ulcerative colitis. *Alimentary Pharmacology & Therapeutics*. 2021;53(5):568-76.
148. Pharmacological Management of Adult Outpatients With Moderate to Severely Active Ulcerative Colitis: Clinical Decision Support Tool. *Gastroenterology*. 2020;158(5):1462-3.
149. Laharie D, Bourreille A, Branche J, et al. Long-term outcome of patients with steroid-refractory acute severe UC treated with ciclosporin or infliximab. *Gut*. 2018;67(2):237-43.
150. Brandse JF, van den Brink GR, Wildenberg ME, et al. Loss of infliximab into feces is associated with lack of response to therapy in patients with severe ulcerative colitis. *Gastroenterology*. 2015;149(2):350-5. e2.
151. Ungar B, Mazor Y, Weisshof R, et al. Induction infliximab levels among patients with acute severe ulcerative colitis compared with patients with moderately severe ulcerative colitis. *Alimentary pharmacology & therapeutics*. 2016;43(12):1293-9.
152. Chao C-Y, Al Khoury A, Aruljothy A, et al. High-dose infliximab rescue therapy for hospitalized acute severe ulcerative colitis does not improve colectomy-free survival. *Digestive Diseases and Sciences*. 2019;64:518-23.
153. Gibson DJ, Doherty J, McNally M, et al. Comparison of medium to long-term outcomes of acute severe ulcerative colitis patients receiving accelerated and standard infliximab induction. *Frontline Gastroenterology*. 2020;11(6):441-7.
154. Gisbert JP, García MJ, Chaparro M. Rescue therapies for steroid-refractory acute severe ulcerative colitis: a review. *Journal of Crohn's and Colitis*. 2023;17(6):972-94.
155. Singh A, Goyal MK, Midha V, et al. Tofacitinib in acute severe ulcerative colitis (TACOS): a randomized controlled trial. *Official journal of the American College of Gastroenterology* | ACG. 2024;119(7):1365-72.
156. Berinstein JA, Karl T, Patel A, et al. Effectiveness of Upadacitinib for Patients with Acute Severe Ulcerative Colitis: A Multi-Center Experience. *Official journal of the American College of Gastroenterology* | ACG. 2022;10.14309.