# IBD Research Review™

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Issue 87 - 2025


## In this issue:



**Abbreviations used in this issue:**

**CD** = Crohn's disease; **IBD** = inflammatory bowel disease; **JAK** = Janus kinase; **PRO** = patient-reported outcome; **UC** = ulcerative colitis.



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## Welcome to issue 87 of IBD Research Review.

We begin this issue with research reporting the development of a microbiome-based test for diagnosing IBD. We then have three phase 3 induction and maintenance trials in moderately to severely active IBD: QUASAR investigated the dual-acting, human IgG1, interleukin-23 p19 subunit inhibitor guselkumab in UC, VIVID evaluated the interleukin-23 p19 inhibitor mirikizumab in CD, and DIVERSITY assessed the oral JAK-1 inhibitor filgotinib in CD. There is also a systematic review and network meta-analysis of the efficacy and safety of biologics and small molecules for the treatment of moderately to severely active UC. This issue concludes with Australian study reporting on the use of metronidazole or vancomycin for treating mild or moderate *Clostridioides difficile* infection in patients with IBD.

We are always appreciative of your comments or feedback.

Kind Regards,


**Dr Alex Barnes**
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## Noninvasive, microbiome-based diagnosis of inflammatory bowel disease

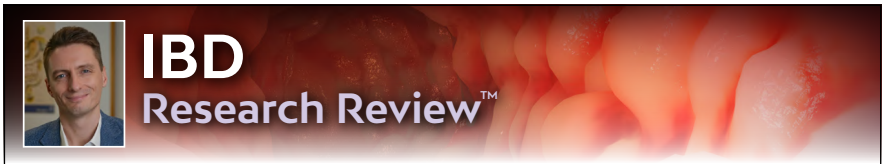
**Authors:** Zheng J et al.


**Summary:** This paper from Hong Kong reported on the development of a microbiome-based test for diagnosing IBD. An analysis of metagenomic data from 5979 faecal samples obtained from patients with and without IBD across a range of ethnicities and geographical locations revealed microbiota alterations in IBD, and ten and nine bacterial species were selected for diagnosing UC and CD, respectively. In a discovery cohort, the diagnostic models had areas under the curves of >0.90 for differentiating IBD from controls, with satisfactory performance maintained in validation cohorts. A multiplex droplet digital PCR test that targeted selected IBD-associated bacterial species was then developed, with models based on this test demonstrating numerically higher performance than faecal calprotectin level for differentiating UC and CD from controls.


**Comment:** This mammoth effort of a study proposed a validated microbial based biomarker for diagnosis of IBD with an area under the curve of 0.81 in validation cohorts, with performance characteristics superior to faecal calprotectin. This study incorporated datasets from eight countries, including China, UK, USA and Australia. The authors also noted adequate performance in distinguishing inactive IBD from active IBD, and have hinted at further work on using this approach to distinguish between different IBD phenotypes. This may represent an alternative to faecal calprotectin for diagnosis and monitoring IBD activity. Obviously this needs independent validation, but further work here appears fruitful.


***Reference: Nat Med 2024;30:3555–67***

Abstract




### Independent commentary by Dr Alex Barnes

Dr Barnes is an academic gastroenterologist with the inflammatory bowel disease unit at Flinders Medical Centre and works privately with IBD SA. Dr Barnes trained at Flinders Medical Centre and the Royal Adelaide Hospital, completing an IBD fellowship at Flinders Medical. He has completed a Masters of Public Health and a PhD examining the significance of sleep disorders in IBD.

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## Guselkumab in patients with moderately to severely active ulcerative colitis (QUASAR)

**Authors:** Rubin DT et al., on behalf of the QUASAR Study Group

**Summary:** This analysis of two randomised phase 3 studies (QUASAR induction and maintenance) in 701 adults with moderate-to-severe active UC and an inadequate response or intolerance to conventional or advanced therapy assessed induction therapy with intravenous guselkumab 200mg (n=421) or placebo (n=280) and maintenance intravenous guselkumab 200mg every 4 weeks (n=190) or 100mg every 8 weeks (n=188) or placebo (n=190) in responders. More guselkumab than placebo recipients experienced clinical remission at induction week 12 (23% vs. 8% [p<0.0001]) and maintenance week 44 (50% and 45% for 200mg every 4 weeks and 100mg every 8 weeks, respectively, vs. 19% [both p<0.0001]). Adverse events were reported by 49% of patients in both treatment groups during induction, with serious adverse events reported by 3% of guselkumab recipients and 7% of placebo recipients; adverse events leading to treatment discontinuation occurred in 2% and 4%, respectively. Adverse event rates were similar across groups during the maintenance study; the most frequent adverse events were UC, COVID-19 and arthralgia.

**Comment:** The paper presents satisfactory efficacy, durability and safety for guselkumab in UC. Yet again, we have another placebo-controlled trial rather than an active comparator. There are of course other p19s although not with CD64 activity. It is notable that an extended induction period did lead to response in 55% of initial nonresponders. We currently have access to seven advanced therapies for UC, and it is unclear where guselkumab will fit. In CD we saw GALAXI 1, 2, 3, and superiority of guselkumab to ustekinumab. Given this, I do wonder how expensive guselkumab will be in Australia.

***Reference: Lancet 2025;405:33–49***
Abstract

## Efficacy and safety of mirikizumab in patients with moderately-to-severely active Crohn's disease

**Authors:** Ferrante M et al., for the VIVID Study Group

**Summary:** Adults with moderately to severely active CD were randomised to receive intravenous mirikizumab 900mg at weeks 0, 4 and 8 then subcutaneous mirikizumab 300mg every 4 weeks for weeks 12–52 (n=579), intravenous ustekinumab ~6 mg/kg at week 0 then subcutaneous ustekinumab 90mg every 8 weeks for weeks 8–52 (n=287) or placebo (n=199) in the phase 3 VIVID trial. Compared with placebo, significantly greater proportions of mirikizumab recipients met the coprimary composite endpoints of patient-reported clinical response at week 12 and endoscopic response at week 52 (38.0% vs. 9.0% [p<0.0001]) and patient-reported clinical response at week 12 and Crohn's Disease Activity Index clinical remission at week 52 (45.4% vs. 19.6% [p<0.0001]). COVID-19 was the most common adverse event across all three study groups. Mirikizumab recipients had lower incidence rates of overall adverse events and discontinuations compared with placebo recipients. The serious adverse event rates in the respective mirikizumab, ustekinumab and placebo arms were 10.3%, 10.7% and 17.1%. None of the three deaths were considered to be study drug-related.

**Comment:** Here we see an active control incorporated with ustekinumab alongside a placebo group. This was a treat-through study with no re-randomisation postinduction, as has been seen in other studies – nonresponders in the placebo group were placed on mirikizumab for the remainder of the study period. Mirikizumab compared with placebo appears effective and safe. In comparison with ustekinumab, it was noninferior for clinical remission and endoscopic response. Mirikizumab did demonstrate superior improvement in the biomarkers calprotectin/C-reactive protein to ustekinumab. Safety was similar to ustekinumab. You may recall SEQUENCE with risankizumab (another p19) and ustekinumab – the trial design was quite different making further comment not possible.

***Reference: Lancet 2024;404:2423–36***
Abstract

## Efficacy and safety of filgotinib as induction and maintenance therapy for Crohn's disease (DIVERSITY)

**Authors:** Vermeire S et al.

**Summary:** Adults with moderately to severely active CD for ≥3 months (n=1372) were enrolled into one of two induction studies according to whether they were biologic-experienced or -naïve. The participants were evenly randomised to receive oral filgotinib 200mg, filgotinib 100mg or placebo once daily for 11 weeks; 481 filgotinib recipients who achieved two-item PRO clinical remission or endoscopic response at week 10 were then re-randomised to receive their induction dose or placebo once daily as maintenance therapy out to week 58. The two-item PRO clinical remission rate at week 10 was greater with filgotinib 200mg than with placebo in biologic-experienced participants (29.7% vs. 17.9% [p=0.0039]) but not in those who were biologic-naïve or later biologic-experienced (32.9% vs. 25.7% [p=0.0963]), and there was no significant difference for endoscopic response at this timepoint in either subgroup. After maintenance therapy, both the two-item PRO clinical remission and endoscopic response rates at week 58 were greater with filgotinib 200mg than placebo (43.8% vs. 26.4% [p=0.0382] and 30.4% vs. 9.4% [p=0.0038], respectively). Filgotinib 100mg conferred no benefit. There were no safety signals for filgotinib.

**Comment:** The study design is somewhat of interest, as there is a claim of a high placebo response rate leading to noninferiority in the induction study. This study incorporated two induction arms: biologic-naïve (A) or biologic-experienced (B) – in reference to predefined biologics (vedolizumab, anti-TNF (tumour necrosis factor), ustekinumab). Each induction arm was then randomised to placebo, filgotinib 100mg or filgotinib 200mg. The 200mg of filgotinib in induction study B did show superiority to placebo for clinical remission but not endoscopic response. Filgotinib failed to demonstrate superiority to placebo in induction study A for any outcome and induction study B for endoscopic response. This is attributed to corticosteroid usage in the placebo arm, although data are not disclosed regarding this – mandatory tapering began in maintenance in this study and not during induction as in other study designs.

***Reference: Lancet Gastroenterol Hepatol 2025;10:138–53***
Abstract

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## Vedolizumab to prevent postoperative recurrence of Crohn's disease (REPREVIO)

**Authors:** D'Haens G et al.

**Summary:** Adults with CD who had undergone ileocolonic resection but were at risk of recurrence were randomised within 4 weeks of surgery to receive intravenous vedolizumab 300mg (evaluable n=43) or placebo (evaluable n=37) at weeks 0, 8, 16 and 24 in the REPREVIO trial. Compared with placebo, the likelihood that vedolizumab recipients had a lower modified Rutgeerts score at week 26 was 77.8% (primary endpoint; p<0.0001), and they had a lower severe endoscopic recurrence rate (23.3% vs. 62.2% [p=0.0004]). The incidences of serious adverse events in the respective vedolizumab and placebo arms were 7.0% and 5.4%.

**Comment:** Unfortunately, again we have a placebo control rather than an active comparator. The population included patients after ileocolonic resection with one or more risk factors for recurrence. Perhaps unsurprisingly, vedolizumab was superior to placebo on Rutgeerts score. The study was performed at 13 sites across four countries, and recruited 84 participants (underwhelming), which perhaps underlies the difficulty of recruitment for these studies. It is notable that the follow-up period was 6 months, and hopefully there is further observation planned. Conclusions are limited.

***Reference: Lancet Gastroenterol Hepatol 2025;10:26–33***
Abstract

## Top-down infliximab plus azathioprine versus azathioprine alone in patients with acute severe ulcerative colitis responsive to intravenous steroids

**Authors:** Amiot A et al.

**Summary:** Thiopurine- and biologic-naïve adults who had been hospitalised for acute severe UC and who were responding to intravenous steroids were randomised to receive azathioprine with (n=32) or without (n=32) infliximab during steroid taper in the open-label ACTIVE trial. An intent-to-treat analysis revealed that compared with azathioprine alone, the addition of infliximab was associated with a lower 52-week treatment failure rate (absence of steroid-free clinical remission or endoscopic response, use of a prohibited treatment for relapse, severe adverse event leading to treatment interruption, colectomy or death; primary outcome; 53.3% vs. 81.5% [p=0.03]). There was no significant difference between the groups for adverse events, which included 13 severe disease exacerbations and six severe infections.

**Comment:** There is a subset of acute severe colitis presentations that do not get started on infliximab during the index admission. Our PBS requirements then delay commencement of advanced therapy for 3 months. This is a difficult study population to recruit – this study included 23 centres in France. As noted, missing data were managed with imputation. Analysis was intention to treat – the azathioprine alone arm had a significant risk ratio for treatment failure; however, this had quite a wide confidence interval and its clinical significance is somewhat unclear. Note that treatment failure was seen in 53% of the infliximab-azathioprine arm – this partly reflects the definition of treatment failure and also the challenges of treating this population. A large study size would be helpful here to allow consideration of other endpoints. Unfortunately, this probably isn't sufficient to challenge PBS requirements.

***Reference: Gut 2025;74:197–205***
Abstract

## Mucosal healing with vedolizumab in patients with chronic pouchitis

**Authors:** Jairath V et al.

**Summary:** Adults with chronic pouchitis were randomised to receive vedolizumab or placebo in the EARNEST trial. Compared with placebo, vedolizumab was associated with a greater decrease from baseline in mean ulcer number at weeks 14 and 34 (respective between-group differences, –8.4 [95% CI –14.3 to –2.6] and–7.0 [–12.0 to –2.0]), as well as greater proportions of participants achieving a reduction in ulcerated pouch surface area (52.4% vs. 20.0% and 52.1% vs. 12.9%), absence of ulceration (23.8% vs. 7.5% and 34.4% vs. 15.6%) and SES-CD (Simple Endoscopic Score for Crohn's Disease) remission (23.8% vs. 7.5% and 34.4% vs. 15.6%) at the respective timepoints, and mucosal healing at week 14 (16.7% vs. 2.5%). Compared with participants who did not achieve mucosal healing at week 14, those who did were more likely to have also achieved remission at this timepoint according to PDAI (Pouchitis Disease Activity Index) and Inflammatory Bowel Disease Questionnaire.

**Comment:** Vedolizumab has been listed on the PBS primarily based on EARNEST – vedolizumab against standard of care in pouchitis – with data presented on improvement in mPDAI, which is primarily a clinical outcome. Data were presented on PDAI endoscopic score and PDAI histological score, with no significant benefit to vedolizumab seen. In this initial publication, they did report SES-CD data and histological data (RHI) as exploratory outcomes, with no differences seen at 34 weeks. Here further analysis from EARNEST is reported, incorporating SES-CD and a definition of mucosal healing incorporating SES-CD and the PDAI histology score, rather than RHI. The results are encouraging, with one-third with SES-CD <2 at 34 weeks – although this was not significantly different to placebo, which may be a study power problem. The created mucosal healing score showed superiority to placebo at week 14, noting that no data from week 34 were reported for mucosal healing – it is unclear why this was. Overall, further larger studies are needed.

***Reference: Lancet Gastroenterol Hepatol 2025;23:321–30***
Abstract

## Efficacy and safety of advanced therapies in moderately-to-severely active ulcerative colitis

**Authors:** Dignass A et al.

**Summary:** This was a systematic review with network meta-analysis of data from 30 randomised controlled trials of biologic and small molecule induction therapies for UC and 22 such trials of maintenance therapies. Among biologic or JAK inhibitor-naïve participants, similar clinical response and remission rates were seen for most induction therapies, but with significantly better improvements with upadacitinib than other interventions, whereas for studies of maintenance therapy, mirikizumab conferred significantly better improvements in terms of clinical response and remission compared with most of the other interventions. Among biologic or JAK inhibitor-experienced participants, there were no significant differences between most interventions among induction studies, except for significantly better clinical response and remission rates for mirikizumab versus adalimumab, and for upadacitinib versus all other interventions; there were few differences seen among active treatments in the maintenance studies. For biologic or JAK inhibitor-experienced and -naïve participants combined, all the active interventions were of similar efficacy with respect to endoscopic mucosal healing, in both the induction and maintenance studies. The serious adverse event rates during induction were similar across all active interventions, irrespective of prior treatment exposure.

**Comment:** There have been several new therapeutic options approved for UC with another network meta-analysis now publishable. Clinical response and remission and mucosal healing were reported on. Differences in study design and definition of mucosal healing were acknowledged. Risankizumab was not included. For induction, upadacitinib demonstrated superiority to most other therapies in biologic-naïve and -experienced patients. For maintenance, there were fewer differences in outcomes between therapies, with mirikizumab demonstrating higher rates of clinical response and remission. Adalimumab once again fared poorly, as did 12-weekly ustekinumab. Analysis of safety was difficult due to the low rate of treatment discontinuation in induction trials. We hope to see mirikizumab in Australia soon.

***Reference: Adv Ther 2024;41:4446–62***
Abstract

## Durable remission after ileocolic resection for Crohn's disease is achievable in selected patients

**Authors:** Abdalla S et al.

**Summary:** Long-term results were reported for the prospective French GETAID Chirurgie cohort study, including 268 patients with CD who had undergone ileocolic resection and had been followed for >36 months (median 85); 59% of the patients had the B2 phenotype, 70% had undergone their first ileocolic resection, and 66% had received medical treatment after surgery. Durable remission (primary outcome) was reported for 19%, 46% of whom didn't require medical treatment and 54% maintained the same postoperative treatment. Surgery stabilised the disease course in 41.7% of patients, including 22.4% endoscopic recurrences that didn't require treatment initiation or intensification. Compared with the B2 or B3 phenotype, patients with the B1 phenotype had a greater durable remission rate (39% vs. 18% [p=0.030]), as did patients who had a first ileocolic resection compared with those who underwent a redo procedure (23% vs. 11% [p=0.023]); however, only B1 phenotype was an independent predictor of durable remission on multivariate analysis (odds ratio 3.59 [95% CI 1.13–11.37]).

**Comment:** Here we have yet another study arguing for ileocolic resection in CD. In those with B1 phenotype, 40% achieved durable remission – defined as more than 36 months post resection without medication escalation or endoscopic recurrence. Half of these were not on any medication. There were unsurprisingly lower rates of medical treatment in the durable remission group, with a higher proportion of this group on a thiopurine alone. This is largely consistent with previous data. Further longer-term data would be helpful, as would larger numbers in the durable remission group, with concerns this is somewhat underpowered. Of note there was a substantial loss to follow-up rate of 22%, and 4% of the cohort were on mesalazine.

***Reference: J Crohns Colitis 2025;19:jjae193***
Abstract

## Treatment outcomes of mild to moderate *Clostridioides difficile* infection in inflammatory bowel disease

**Authors:** Jacob R et al.

**Summary:** This retrospective Australian research compared treatment outcomes for metronidazole versus vancomycin in 18 patients with CD, 15 with UC and one with IBD unclassified who collectively had 47 discrete mild or moderate *C. difficile* infections between Jan 2015 and Dec 2019. Around two thirds of the patients (68%) were prescribed metronidazole and 23% were prescribed vancomycin. For the respective metronidazole and vancomycin groups, treatment failure rates were 20% and 0%, *C. difficile* infection recurrence rates were 13% and 10%, and 20% and 40% experienced a further episode of *C. difficile* infection, but none of the differences were statistically significant. The only factor associated with a higher risk of a composite of these outcomes was proton pump inhibitor therapy (adjusted odds ratio 12.99 [95% CI 1.21–139.97]).

**Comment:** This was a single-centre Australian study reporting real-world data on treatment of mild or moderate *C. difficile* infection in IBD. No difference in outcomes was seen between metronidazole and vancomycin. Successful treatment of *C. difficile* infection was achieved with metronidazole in 80%. No *C. difficile* infection episode required colectomy or faecal microbiota transplantation. Proton pump inhibitor usage was associated with an increased odds of combined outcome of treatment failure and *C. difficile* infection recurrence. No other Australian data have been reported in this area. There are obvious power concerns leading to limited conclusions.

***Reference: Intern Med J 2024;54:2009–14***
Abstract



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