South African National Department of Health
Limited Review - infliximab for acute ulcerative colitis
Component: Tertiary and Quaternary Hospital Level

TITLE: Infliximab for patients with acute, severe steroid refractory, ulcerative colitis

Date: October 2024

Medicine (ATC): Tumour Necrosis Factor Alpha inhibitors (anti-TNFs): Infliximab (L04AB02)
Indication (ICD10): Ulcerative colitis, unspecified (K51.9)
Patient population: Patients of all ages with acute, severe ulcerative colitis (UC) who are refractory to intravenous corticosteroids.
Prevalence: There is a paucity of South African data. A study conducted in 1984 reported incidence rates for UC among the coloured, white and black population groups as 1.9, 5.0 and 0.6/100 000 per year, respectively.[1] Based on expert opinion, it is estimated that only a small number of patients would present with severe, acute UC and refractory to corticosteroids (approximately 10 patients)[i]
Level of Care: Tertiary and Quaternary Hospital Level
Prescriber level: Gastroenterologist
Current Standard of Care/ Comparator(s): Conventional therapy: intravenous corticosteroids

Key findings

- Conventional therapies for Ulcerative Colitis (UC) listed on the Essential Medicines List (EML) include azathioprine (oral), sulfasalazine (oral), intravenous and oral corticosteroids and mesalazine suppositories. Intravenous corticosteroids are standard of care for patients with acute, severe UC.
- A motivation was received to include Tumour Necrosis Factor Alpha (anti-TNFs) Inhibitors, specifically infliximab, onto the EML for individuals with ulcerative colitis who are refractory to conventional therapies. The motivation included infliximab as rescue therapy for patients with acute, severe UC refractory to corticosteroid therapy.
- We conducted a review of the literature to explore the safety and efficacy of the addition of infliximab to standard of care compared to standard of care alone for patients with acute, severe UC who are refractory to intravenous corticosteroids. We extracted data from 6 publications (1 SRs, and 5 guidelines).
- **Comparison 1: Infliximab vs Standard of care**
  - Rate of colectomy 1 month or less after treatment
    Infliximab was found to be more beneficial than placebo for reducing need for colectomy at 1 month or less (RR 0.37; 95% CI [0.21 to 0.65], i^2=0%, Probability of being the most efficacious = 82%; 7 RCTs, n=534) – low certainty of evidence.
  - Clinical response and remission
    Fewer infliximab receiving participants failed to respond to therapy (as defined by the study) as compared to placebo (RR 0.48; 95% CI [0.30 to 0.77], i^2=0%; Probability of being the most efficacious = 67%, 5 RCTs, n=459) – low certainty of evidence.
  - Safety
    There were more serious adverse events observed in the placebo compared to infliximab however the estimate crossed the line of no effect (RR 0.63; 95% CI [0.20 to 1.98], i^2=8.6%, – no statistically significant difference; Probability of being the best = 54%, 7 RCTs, n=534).

[i] Estimate provided by Prof G Watermeyer, personal email communication.

- Moderate to high quality guidelines recommend infliximab for acute severe CD who are refractory to conventional therapy.
- The intervention is incrementally more costly than the standard of care however costs are likely offset by delay in need for extended acute hospital care and surgery.
- **Recommendation:**
  The Tertiary/Quaternary Expert Review Committee suggests using infliximab as rescue therapy for patients (adults and children) with acute, severe ulcerative colitis who are refractory to intravenous corticosteroids.

See Appendix A for evidence to decision framework

TERTIARY AND QUATERNARY EXPERT REVIEW COMMITTEE RECOMMENDATION:

Type of recommendation	We recommend against the option and for the alternative **(strong)**	We suggest not to use the option or to use the alternative **(conditional)**	We suggest using either the option or the alternative **(conditional)**	We suggest using the option **(conditional)**	We recommend the option **(strong)**
				X	

The Tertiary and Quaternary Expert Review Committee suggests using infliximab as rescue therapy for patients (adults and children) with acute, severe ulcerative colitis, who are refractory to intravenous corticosteroids.

Rationale: Acute, severe ulcerative colitis is a medical emergency, and in patients where intravenous corticosteroid therapy has failed there is a need for a next line of therapy to prevent morbidity, surgery and increased resource requirements in these patients. Although the evidence is of lower quality, rescue therapy with infliximab compared to placebo was shown to effective in reducing rate of colectomy one month or less after receiving treatment and in achieving response to therapy. No difference in serious adverse events was observed.

Monitoring: Although there was limited evidence to show concerns regarding safety around infections, in the South African potential increased risk of infection such as TB is an important consideration for monitoring and initiating treatment. However, due to the urgency of the condition, assessment for latent or active tuberculosis is not always feasible prior to treatment initiation. Furthermore, treatment is of short duration (one or two doses).

Level of Evidence: Low Quality Systematic reviews (AMSTAR 2), evidence certainty considered to be low for infliximab compared to placebo.

NEMLC RECOMMENDATION: 10th October 2024
NEMLC supports the inclusion of infliximab as rescue therapy for acute, severe ulcerative colitis, refractory to intravenous steroids for patients 6 years and older.

Review Indicators: Price, change in evidence of safety or efficacy

Overview

Motivations for inclusion of TNF-inhibitors for adults and children with ulcerative colitis (UC) and Crohn's Disease (CD) were received and the topics prioritised for review.[2,3] Medicine reviews for CD were undertaken separately (See medicine reviews for fistulising CD – PICO 1[4] and luminal CD – PICO 2[5]). Conventional therapy for UC was identified as a gap on the EML and this was addressed through the historically accepted use mechanism (NEMLC May 2024). Standard of care on the Tertiary and Quaternary Hospital Level EML for UC now includes azathioprine (oral), sulfasalazine (oral), intravenous and oral corticosteroids and mesalazine suppositories.[6]

This particular review is focussed on patients with acute, severe UC (ASUC). Patients with ASUC are considered a medical emergency, and standard of care first line therapy is intravenous corticosteroids. However, for those patients who are refractory to intravenous corticosteroids, an alternative option is required as salvage medical therapy to an attempt to delay surgery. [7] Infliximab is a potential option for this specific patient group with the aim to re-establish the patient on conventional maintenance therapy. Ciclosporin is an alternative therapy recommended in some guidelines however is not routinely used in South Africa on account of associated adverse events and difficulty associated with patient monitoring. [1,2] Moreover, the medication is not licenced for this indication and is not currently on tender.[8]

Based on expert opinion, the potential population number are expected to be small. It was estimated that there may only be around 60 patients per year with inflammatory bowel disease nationally who would be refractory to conventional therapy based on a national survey. Of this number, 10% are estimated to be ulcerative colitis patients and an even lower percentage acute, severe patients. A limited, rapid review of systematic reviews and clinical guidelines was thus conducted to assess the benefit of infliximab in the management of patients with ASUC.

RESEARCH QUESTION:

What is the efficacy and safety of infliximab as rescue therapy for individuals with acute, severe ulcerative colitis, who are refractory to intravenous corticosteroids.

METHODS

Eligibility criteria for review

Table 1: Proposed PICO

Population:	Patients with acute, severe ulcerative colitis* who are refractory to intravenous corticosteroids**
Intervention:	Biologics targeting Tumour Necrosis factor-α (anti-TNFs) namely infliximab 5mg/kg
	• Single infusion (0 weeks), • Double infusion (0 and 2 weeks)
Comparators:	• Placebo
Outcomes:	1) Reduction in rate of surgeries (short timeframe) 2) Response to therapy (short timeframe) 3) Safety
Study designs	Systematic reviews of RCTs, clinical guidelines

* According to the American Gastroenterological Association (AGA), ASUC was defined as "hospitalized patients with the following Truelove and Witts criteria: 6 or more bloody bowel movements/day with at least 1 marker of systemic toxicity, including heart rate >90 beats/min, temperature >37.8C, haemoglobin <10.5 g/dL, and/or erythrocyte sedimentation rate –30 mm/h"[9].

**Considered as no response after three days of intravenous corticosteroid therapy. Definition utilised in The European Crohn's and Colitis Organisation (ECCO) guidelines as "Failure may be predicted using the Travis criterion,13 which combines the number of stools after 3 days of corticosteroid therapy and the level of serum CRP"[10].

Methods

A rapid search of Systematic Reviews (SRs) and Clinical Practice Guidelines (CPGs) was conducted in September 2024 in PubMed, Cochrane and Guidelines International Network (G-I-N) databases - See Appendix B for search strategy. A targeted google search was also conducted for CPGs utilising combination of search terms 'acute severe', 'ulcerative colitis', 'rescue therapy', and 'infliximab'. Titles and abstracts of documents were screened independently in duplicate with conflicts resolved by discussion (KM and JR). Full text review was undertaken by one reviewer (KM) and checked by a second reviewer (JR). Selected SRs were evaluated with AMSTAR II[11] (independently, in duplicate - KM and JR) and CPGS were evaluated in duplicate by two reviewers with AGREE II (KM, JR or DR). [12]

Results

The search for systematic reviews and clinical guidelines resulted in 164 documents, after removal of 3 duplicates and screening, 20 documents remained. After full text review, only one SR (by Barberio et al. 2021[13]), and five guidelines remained that met the study PICO (6 documents in total) - See Figure 1 PRISMA diagram). See Appendix C for list of excluded studies.

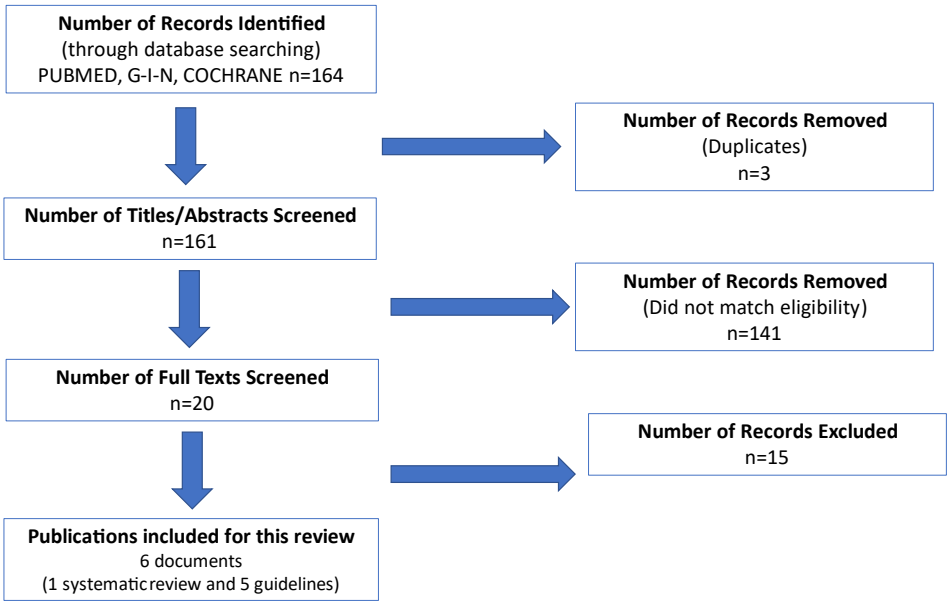


Figure 1: PRISMA Diagram

Barberio 2021[13] reported on a SR and network meta-analysis (NMA) of randomised-controlled trials (RCTs) – See **Table 2** below for details of the included SR and **Tables 3 and 4** for characteristics of the RCTs included within the Barberio 2021 SR. [13] See Guidelines Section for details on included CPGs.

Table 2: Characteristics of include SR

Author	Study Type	Population	Intervention & Comparators	Outcomes
Barberio 2021[13]	SR and MR of RCTs – 7 RCTs, 534 participants.	Acute, steroid refractory, moderate to severe UC Adults - eligibility criteria that >90% of included	• Infliximab, IV (single or double dose) vs placebo • Cyclosporine, IV daily dose for two weeks vs placebo • Infliximab, IV (triple dose) vs cyclosporin, IV daily for	Colectomy rates at ≤1 month (7 RCTs, n=534) • Infliximab vs placebo RR 0.37; 95% CI [0.21 to 0.65], Probability of being the most efficacious = 82%. Response to therapy – Failure to respond (5 RCTs, n=459)

		population needed to be 18 years or older	a week followed by oral for 3 months • Infliximab, IV (triple dose) vs cyclosporin, oral daily	• Infliximab vs placebo RR 0.48; 95% CI [0.30 to 0.77], Probability of being the most efficacious = 67%. <u>Serious adverse events (7 RCTs, n=534)</u> • Infliximab vs placebo RR 0.63; 95% CI [0.20 to 1.98], – no statistically significant difference; Probability of being the best = 54%.

Internal validity and Risk of Bias

The SR was evaluated to be of low quality when assessed with AMSTAR II (See Appendix D). Some components of the review were rated as "strong" such as screening, study selection done independently and clear discussion on risk of bias of studies. However other components were lacking such as not including funding sources of the selected studies and a list of excluded studies with reasons (other than grouped reason within the PRIMSA diagram). To note that the SR population was slightly wider ie. **moderate to severe**, acute steroid refractory UC.

Barberio 2021[13] conducted Risk of Bias 1 (RoB1) on all the included studies. All trials, except one (Scimeca 2012), were published in full. None of the studies was evaluated as low risk of bias overall. The three RCTs which included infliximab versus placebo (Sands 2001, Probert 2003, Jarnerot 2005 & Gustavsson 2010) did not have any domains evaluated as high risk of bias but had at least one domain categorised as unclear risk. The three RCTs included which evaluated infliximab compared to ciclosporin (Laharie 2012, 2017, Scimeca 2012, Williams 2016) had one domain (blinding) categorised as high risk. See Table 5 below.

Table 5 – Risk of bias evaluation of studies included in Barberio 2021[13], extracted from SR.

Study and year	Generation of Randomization	Concealment of Treatment Allocation	Blinding	Incomplete Outcomes Data	Selective Reporting of Outcomes
Lichtiger 1994	**Unclear**	**Unclear**	**Low**	**Low**	**Low**
Sands 2001	**Unclear**	**Unclear**	**Low**	**Low**	**Low**
Probert 2003	**Unclear**	**Low**	**Low**	**Low**	**Low**
Jarnerot 2005 & Gustavsson 2010	**Unclear**	**Low**	**Low**	**Low**	**Low**
Laharie 2012 and Laharie 2017	**Low**	**Low**	**High**	**Low**	**Low**
Scimeca 2012	**Unclear**	**Unclear**	**High**	**Low**	**Low**
Williams 2016	**Low**	**Low**	**High**	**Low**	**Low**

Table 3 – Characteristics of studies included in Barberio 2021[13]

Table 2. Characteristics of randomized controlled trials of infliximab or ciclosporin vs placebo or each other in acute moderate to severe UC

Study and year	Country, and number of centres	Disease distribution	Endpoints reported	Total number of patients	Treatments compared [number of patients in each arm]	Duration of follow up
Lichtiger 1994[8]	USA, 2 sites	80% pancolitis, 20% left-sided	Response to therapy [Lichtiger score < 10 on 2 consecutive days] Colectomy rate at ≤ 1 month	20	Infusion of ciclosporin 4 mg/kg/day [11] vs placebo [9] for up to 2 weeks	1 month
Sands 2001[23]	USA and Belgium, multiple sites	Not reported	Response to therapy [Truelove and Witts severity score < 10 with a 5-point decrease from baseline] Colectomy rate at ≤ 1 month, and between > 1 month and < 1 year	11	Single infusion of infliximab 5, 10 or 20 mg/kg [8] vs placebo [3]	3 months
Probert 2003[24]	UK and Germany, 4 sites	62% pancolitis, 19% left-sided, and 19% proctosigmoiditis or proctitis	Response to therapy [≥1-point decrease in Baron score from baseline] Remission [ulcerative colitis symptom score ≤ 2] Colectomy rate at ≤ 1 month, and between > 1 month and < 1 year	43	Two infusions of infliximab 5 mg/kg at 0 and 2 weeks [23] vs placebo [20]	8 weeks
Jarnerot 2005[10] and Gustavsson 2010[25]	Sweden and Denmark, 10 sites	80% pancolitis, 20% proctosigmoiditis or proctitis	Colectomy rate at ≤ 1 month, between > 1 month and < 1 year, and ≥ 1 year	45	Single infusion of infliximab 5 mg/kg [24] vs placebo [21]	3 years
Laharie 2012[11] and Laharie 2017[26]	Multinational, 27 sites	57% pancolitis, 43% left-sided, proctosigmoiditis, or proctitis	Response to therapy [Lichtiger score < 10 points with a 3-point decrease from baseline] Remission [mucosal healing] Colectomy rate at ≤ 1 month, between > 1 month and < 1 year, and ≥ 1 year	115	Infusion of ciclosporin 2 mg/kg/day for 1 week followed by oral ciclosporin until day 98 [58] vs three infusions of infliximab 5 mg/kg at 0, 2 and 6 weeks [57]	5 years
Scimeca 2012[27]	Italy, 1 site	80% pancolitis, 20% left-sided	Remission [Powell-Tuck index ≤ 3] Colectomy rate at ≤ 1 month, and ≥ 1 year	30	Oral ciclosporin 5 mg/kg/day [13] vs three infusions of infliximab 5 mg/kg at 0, 2 and 6 weeks [17]	1 year
Williams 2016[12]	UK, 52 sites	46% pancolitis, 47% left-sided, and 7% proctitis	Response to therapy Colectomy rate at ≤ 1 month, between > 1 month and < 1 year, and ≥ 1 year	270	Infusion of ciclosporin 2 mg/kg/day for 1 week followed by oral ciclosporin for 12 weeks [135] vs three infusions of infliximab 5 mg/kg at 0, 2 and 6 weeks [135]	1–3 years

Table 4 Efficacy estimates for infliximab versus placebo studies included in Barberio 2021[13]

Study	Note	Outcomes and estimates
Sands 2001[14]	11 patients only (8 infliximab and 3 placebo), older than 17 but younger than 65 years of age. * All patients had severe, active UC as defined by a modification of the Truelove and Witts classification of severity of UC *Patients had received at least 7 days of corticosteroid therapy of which at least 5 days included intravenous administration.	Clinical Response at 2 weeks (modified Truelove and Witts criteria) None of the placebo treated patients (0/3 = 0%) and four of the infliximab-treated patients (4/8 = 50%) were classified as responders **RR 4** 95% CI [0.28 to 58], P = 0.3095, estimate crosses line of no effect[ii]. Colectomy at 2 weeks All the placebo patients underwent colectomy (100%) compared to only one patient from the infliximab groups (14%) at 2 weeks **RR 0.13** 95% CI [0.02 to 0.78], P = 0.026, **NNT 2** 95% CI [1 (Benefit) to 2.0 (Benefit). [ii]
Probert 2003[15]	43 patients (23 infliximab and 20 placebo) *Patients were excluded from the trial if they had fulminant disease likely to require colectomy. *Focussed on moderate acute ulcerative colitis *Time period 6 weeks	One patient in the placebo group (1/20; 5%) and no patients in the infliximab group (0/23;0%) underwent colectomy during the study period (6 weeks) **RR 3.27** 95% CI [0.14 to 76.22], P= 0.46, estimate crosses line of no effect [ii].
Jarnerot 2005[16]	Forty-five patients were included (24 infliximab and 21 placebo). Ages ≥18 or ≤75 years. *At hospitalization, patients had a severe or moderately severe attack of UC according to the Seo index. For treatment with infliximab/placebo, the patients had to have a fulminant colitis index >8.0 on day 3 after institution of IIVT or a Seo index on day 5, 6, or 7 that was compatible with a severe or moderately severe attack of UC that was not responding to corticosteroid treatment.	Colectomy at 90 days Seven patients in the infliximab group (7/24 = 29%) and 14 in the placebo group (14/21 = 67%) had a colectomy within 3 months after randomization (P = 0.017; OR 4.9; 95% CI [1.4 –17). Operations occurred for all patients (both groups) within the first month. **RR 0.44** 95% CI [0.22 to 0.88], P=0.0194, **NNT 3** 95% CI [1.55 (benefit) to 10 (benefit).[ii] Death at 90 days No patient died. No serious side effects occurred. Three patients in the placebo group required operation for septic complications.

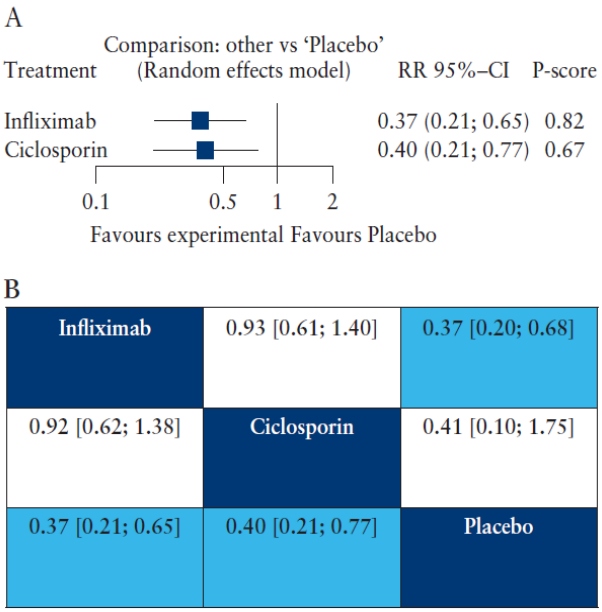
[ii] Calculations undertaken with online calculator (https://www.medcalc.org/calc/relative_risk.php) based on estimated provided in articles

Efficacy

1. Infliximab compared to placebo

1.1. Rate of colectomy at 1 month or less

Infliximab was reported by the Barberio 2021 SR[13] to be more beneficial than placebo for reducing need for colectomy at 1 month or less (RR 0.37; 95% CI [0.21 to 0.65], i^2=0%, Probability of being the most efficacious = 82%; 7 RCTs, n=534) – See Figure 2.



Network meta-analysis of likelihood of colectomy at < 1 month. [A] Forest plot showing the relative risk of colectomy at < 1 month. The P-score is the probability of each treatment being ranked as best in terms of efficacy in the network. [B] League table of pairwise comparisons in the network meta-analysis for the relative risk of colectomy at < 1 month. Relative risk with 95% confidence intervals in parentheses. Comparisons, column vs row, should be read from left to right, and are ordered relative to their overall efficacy. The treatment in the top left position is ranked as best after the network meta-analysis of direct and indirect effects. Boxes highlighted in light blue indicate significant differences. Direct comparisons are provided above the drug labels, and indirect comparisons are below.

Figure 2 – Colectomy at ≤ 1 month forest plot and league table from Barberio 2021[13]

1.2. Clinical response to therapy

The SR[13] reported that less infliximab receiving participants failed to respond to therapy (as defined by the study) as compared to placebo (RR 0.48; 95% CI [0.30 to 0.77], i^2=0%, Probability of being the most efficacious = 67%, 5 RCTs, n=459) – See figure 3. To note that timeframes for response to therapy differed in the included studies. It is unclear which exact estimates were utilised as this outcome was not categorised in the same manner as rate of colectomy.

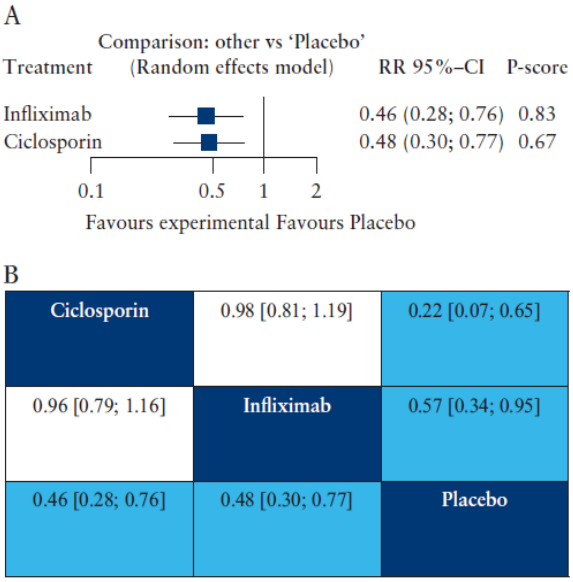


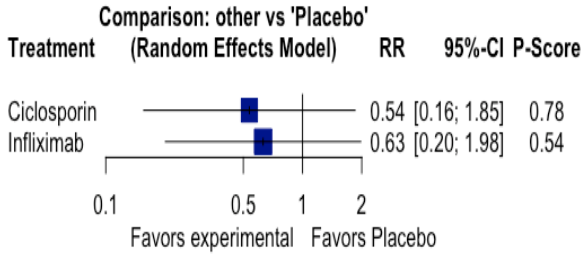
Figure 4. Network meta-analysis of failure to achieve a response to therapy. [A] Forest plot showing the relative risk of failure to achieve a response to therapy. The P-score is the probability of each treatment being ranked as best in terms of efficacy in the network. [B] League table of pairwise comparisons in the network meta-analysis for the relative risk of failure to achieve a response to therapy. Relative risk with 95% confidence intervals in parentheses. Comparisons, column vs row, should be read from left to right, and are ordered relative to their overall efficacy. The treatment in the top left position is ranked as best after the network meta-analysis of direct and indirect effects. Boxes highlighted in light blue indicate significant differences. Direct comparisons are provided above the drug labels, and indirect comparisons are below.

Figure 3 – Failure to achieve a response to therapy – Barberio 2021[13]

1.3. Safety

There were more serious adverse events observed in the placebo compared to infliximab however the estimate crossed the line of no effect (RR 0.63; 95% CI [0.20 to 1.98], i^2=8.6%, – no statistically significant difference; Probability of being the best = 54%, 7 RCTs, n=534) – See Figure 4.

A.



B.

Ciclosporin	**0.81 [0.46; 1.42]**	**2.48 [0.11; 55.61]**
0.85 [0.49; 1.48]	**Infliximab**	**0.50 [0.15; 1.69]**
0.54 [0.16; 1.85]	**0.63 [0.20; 1.98]**	**Placebo**

(A) Forest plot showing the relative risk of serious adverse events. The P score is the probability of each treatment being ranked as best in terms of efficacy in the network.

(B) League table of pairwise comparisons in the network meta-analysis for the relative risk of serious adverse events. Relative risk with 95% confidence intervals in parentheses. Comparisons, column versus row, should be read from left to right, and are ordered relative to their overall efficacy. The treatment in the top left position is ranked as best after the network meta-analysis of direct and indirect effects. Boxes highlighted in light blue indicate significant differences. Direct comparisons are provided above the drug labels, and indirect comparisons are below.

Figure 4: Serious adverse events from Barberio 2021[13]

Quality and Certainty of Evidence

Barberio 2021[13] did conduct RoB1 on included studies (See Results section). It was reported that included studies that evaluated infliximab versus placebo directly had an unclear risk of bias for one or two domains and no domains with high risk of bias. The domain for blinding was categorised as high risk of bias for RCTs comparing infliximab and ciclosporin directly, however other domains were low or unclear risk of bias. The PICO of the SR and the studies included which evaluated infliximab and placebo directly, met the medicine review PICO very closely (only difference was wider population of moderate to severe acute rather than only severe patients, however all were refractory to steroids). Sample sizes for studies that are infliximab vs placebo directly were small however limitation around conducting RCTs for this specific indication is noted. Little or no heterogeneity detected in the analyses. Overall the quality of evidence was considered to be low overall.

Guidelines

Five guidelines met the PICO and were included for extraction and assessed with AGREE II. All the guidelines except the NICE 2019[19] guidance focussed only on adults. Overall quality was moderate to high with the American Gastroenterological Association (AGA)[17] and NICE guidelines scoring the highest for rigour and methodology. Only one guideline (Polish Society of Gastroenterology and the Polish National Consultant in Gastroenterology)[21] scored less than 60% overall. In particular, the domain on rigour received a low score due to lack of transparency and details regarding methodology. See Table 6 for details.

Table 6: Details of included guidelines

Guideline	Recommendation	Strength of recommendation and Quality	AGREE II
AGA Clinical Practice Guidelines on the Management of Moderate to Severe Ulcerative Colitis[17]	**10.** In hospitalized **adult** patients with ASUC refractory to intravenous corticosteroids, the AGA suggests using infliximab or cyclosporine.	Conditional, Low	**Overall assessment score:** 74%, 6 out of 7 **Score for rigour and methodology domain:** 86%
	11. In hospitalized **adult** patients with acute severe UC being treated with infliximab, the AGA makes no recommendation on routine use of intensive vs standard infliximab dosing.	No recommendation, Knowledge gap	
ECCO Guidelines on Therapeutics in Ulcerative Colitis: Surgical Treatment[18]	**Statement 1.1.** Intravenous corticosteroids as the initial standard treatment for **adult** patients with ASUC are recommended, as this treatment induces clinical remission and reduces mortality.	**EL3** *[EL2 (randomized controlled trial) was downgraded because of high RoB*]*	**Overall assessment score:** 68%, 5 out of 7 **Score for rigour and methodology domain:** 68%
	Statement 1.2. Either infliximab or cyclosporine should be used in **adult** patients with steroid-refractory ASUC. When choosing between these strategies, centre experience and a plan for maintenance therapy after cyclosporine should be considered.	**EL3** *[Evidence derived from systematic reviews, meta-analysis and RCTS but downgraded due to RoB, imprecision and publication bias]*	
	Statement 1.3. There is currently insufficient evidence to determine the optimal regimen of infliximab rescue therapy in patients with ASUC refractory to corticosteroid therapy.	**EL4** *[EL3 (SR evidence from observational studies is initially classified as low-quality) was downgraded because of serious RoB*]*	
NICE 2019 Ulcerative colitis: management ng130[19]	<u>Treating acute severe ulcerative colitis: all extents of disease</u> <u>Step 1 therapy</u> 1.2.16 **For people** admitted to hospital with acute severe ulcerative colitis (either a first presentation or an inflammatory exacerbation): • offer intravenous corticosteroids to induce remission 1.2.17 Consider intravenous ciclosporin or surgery for people: • who cannot tolerate or who decline intravenous corticosteroids or • for whom treatment with intravenous corticosteroids is contraindicated. Take into account the person's preferences when choosing treatment. [2013] In May 2019, this was an off-label use of ciclosporin. <u>Step 2 therapy</u> 1.2.18 Consider adding intravenous ciclosporin to intravenous corticosteroids or consider surgery for people: • who have little or no improvement within 72 hours of starting intravenous corticosteroids or • whose symptoms worsen at any time despite corticosteroid treatment. Take into account the person's preferences when choosing treatment. [2013] In May 2019, this was an off-label use of ciclosporin.	Strong recommendations based on weak evidence	**Overall assessment score:** 81%, 6 out of 7 **Score for rigour and methodology domain:** 81%

	1.2.19 Infliximab is recommended as an option for the treatment of acute exacerbations of severely active ulcerative colitis only in patients in whom ciclosporin is contraindicated or clinically inappropriate, based on a careful assessment of the risks and benefits of treatment in the individual patient. [2008] [This recommendation is from NICE technology appraisal guidance on infliximab for acute exacerbations of UC]		
Update of the PANCCO clinical practice guidelines for the treatment of ulcerative colitis in the **adult** population[20]	**Recommendation No. 7:** The use of intravenous cyclosporine is recommended for inducing remission in patients with acute severe UC that is refractory to intravenous steroids. Good practice point: Cyclosporine or infliximab can be used in patients with acute severe UC that is refractory to intravenous steroids. Good practice point: Intravenous cyclosporine should be administered at a dose of 2 mg/kg/day. Good practice point: Intravenous cyclosporine should only be administered at specialized complex care centers by professionals with experience in its use.	Conditional, in favor of the strategy. GRADE Quality of evidence ⊕⊕ - low.	**Overall assessment score:** 75%, 5 out of 7 **Score for rigour and methodology domain:** 75%
	Recommendation No. 15: The use of infliximab is recommended for managing patients with acute severe UC that is refractory to IV corticoids.	Strong, in favor of the strategy. GRADE Quality of evidence ⊕ - very low.	
	Recommendation No. 16: The routine use of an intensified regimen of infliximab is not recommended in patients with acute severe UC. Good practice point: An intensified regimen of infliximab can be considered as acute rescue therapy. Good practice point: An initial dose of 5 mg/kg of infliximab is preferred to 10 mg/kg, in the multiple dose regimen.	Conditional, against the strategy. GRADE Quality of evidence ⊕ - very low.	
Guidelines for the management of ulcerative colitis. Recommendations of the Polish Society of Gastroenterology and the Polish National Consultant in Gastroenterology[21]	**14.** We suggest IV steroid treatment in the hospital setting of **patient**s who meet the Truelove and Witts criteria for acute severe UC.	(Quality of evidence: very low; strength of recommendation: weak); Likert scale 100% complete approval	**Overall assessment score:** 54%, 4 out of 7 **Score for rigour and methodology domain:** 44%
	15. We recommend infliximab in **patient**s who have not responded to 3 days of intravenous steroid therapy. As an alternative to infliximab, ciclosporin may be used. ***adult patients (over 18 years)**	(Quality of evidence: moderate; strength of recommendation: strong); Likert scale 34% approval, 66% Complete approval	

Costs

Table 7 outlines the cost per patient as well as the potential budget impact. The cost of surgery and hospitalisation has not been considered and is likely to offset estimated costs of infliximab.

Table 7: Cost per patient and estimated budget impact per annum

Dose mg/kg	Dose mg*	Product	Strength	No	Price per vial**	Cost per single dose	Cost per two dose regimen	No. of patients	Total budget p/annum (single dose)	Total budget p/annum (double dose)
5	350	Remsima	100	4	R2 593	R10 373	R20 747	10	R103 730	R207 470
5	350	Remiflix	100	4	R2 593	R10 373	R20 747	10	R103 730	R207 470
5	350	Revellex	100	4	R3 251	R13 004	R26 009	10	R130 040	R260 090

*70kg weight, **Price based on SEP – August 2024

Conclusion

Acute, severe ulcerative colitis is considered a medical emergency. In patients where intravenous corticosteroid therapy has failed, there is a need for a next line of therapy to prevent morbidity, surgery and increased resource requirements in these patients. Although the evidence is of lower quality, rescue therapy with infliximab compared to placebo was shown to be effective in reducing the rate of colectomy one month or less after receiving treatment and in achieving response to therapy. No difference in serious adverse events was observed. Moderate to high quality guidelines recommend infliximab in this setting as does the South African Gastroenterology Society (SAGES) in their position paper.[22] Although no specific evidence was found for paediatrics, the NICE guidelines indicate that infliximab could be utilised in children older than 6 years and the SAGES guidelines do not specify age limits. Moreover, infliximab is licenced for adult and paediatric ulcerative colitis.[23] The Tertiary and Quaternary Expert Review Committee thus suggests using infliximab as rescue therapy for patients (adults and children) with acute, severe ulcerative colitis, who are refractory to intravenous corticosteroids.

Reviewers: Kim MacQuilkan, Jane Riddin, Roger Wiseman, Marc Blockman

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- Gillian Watermeyer – support with formulation of PICO and patient estimates.
- Derusha Frank – support with AGREE II assessments

Declaration of interests:

- Kim MacQuilkan (GH-SCTA) has no interests to declare
- Jane Riddin (Essential Drugs Programme) has no interests to declare
- Roger Wiseman (Liberty Health (Pty) Ltd, South Africa) has no interests to declare.
- Marc Blockman (Department of Clinical Pharmacology, Groote Schuur Hospital, Cape Town, Western Cape, South Africa and the Department of Medicine, University of Cape Town, Cape Town, Western Cape, South Africa). Has no interests to declare
- Gillian Watermeyer (Department of Gastroenterology, Groote Schuur Hospital, Cape Town, Western Cape, South Africa and the Department of Medicine, University of Cape Town, Cape Town, Western Cape, South Africa). Has no interests to declare but to note that GM works with CD patients and uses TNF-inhibitors.
- Derush Frank (CHAI) has no interests to declare

Appendix A: Evidence to decision framework

	JUDGEMENT	EVIDENCE & ADDITIONAL CONSIDERATIONS
EVIDENCE OF BENEFIT	**What is the certainty/quality of evidence?** High ☐ Moderate ☐ Low ☒ Very low ☐	*Results extracted from Low quality SR (AMSTAR 2)* **Comparison 1: Infliximab vs placebo** *Overall quality of evidence considered low for all outcomes* 1.1. **Rate of Colectomy less than a month** – SR of RCTs, downgraded for unclear/high risk of bias in some studies, small sample but no issues with heterogeneity or directness 1.2. **Response to therapy** – SR of RCTs, downgraded for unclear/high risk of bias in some studies, small sample but no issues with heterogeneity or directness.
EVIDENCE OF BENEFIT	**What is the size of the effect for beneficial outcomes?** Large ☐ Moderate ☒ Small ☐ None ☐	**Comparison 1: Infliximab vs placebo** 1.1 **Rate of Colectomy less than a month** – Infliximab vs placebo (RR 0.37; 95% CI [0.21 to 0.65], i^2=0%, Probability of being the most efficacious = 82%; 7 RCTs, n=534). 1.2 **Response to therapy** Infliximab vs placebo (RR 0.48; 95% CI [0.30 to 0.77], i^2=0%, Probability of being the most efficacious = 67%, 5 RCTs, n=459). NNT from underlying studies (note not an exact match for how outcomes presented in the review for timeframe)[ii] • Sands 2001[14]: Colectomy at two weeks (severe acute UC); RR 0.13 95% CI [0.02 to 0.78], P = 0.026, **NNT 2** 95% CI [1 (Benefit) to 2.0 (Benefit). • Probert 2003[15] : Colectomy at six weeks (moderate acute UC); RR 3.27 95% CI [0.14 to 76.22], P= 0.46, estimate crosses line of no effect). • Jarnerot 2005[16] : Colectomy at 90 days (moderate to severe acute UC); RR 0.44 95% CI [0.22 to 0.88], P=0.0194, **NNT 3** 95% CI [2 (benefit) to 10 (benefit).

	JUDGEMENT	EVIDENCE & ADDITIONAL CONSIDERATIONS
EVIDENCE OF HARMS	**What is the certainty/quality of evidence?** High ☐ Moderate ☐ Low ☒ Very low ☐	*Results extracted from low quality SR (AMSTAR 2)* **Comparison 1: Infliximab vs placebo** *Overall quality of evidence considered low* 1.3. **Serious adverse events -** SR of RCTs, downgraded for unclear/high risk of bias in some studies, small sample but no issues with heterogeneity or directness
EVIDENCE OF HARMS	**What is the size of the effect for harmful outcomes?** **L**arge ☐ Moderate ☐ Small ☐ None ☒	**Comparison 1: Infliximab vs placebo** **1.3 – Serious adverse events** There were more serious adverse events observed in the placebo compared to infliximab however the estimate crossed the line of no effect (RR 0.63; 95% CI [0.20 to 1.98], i^2=8.6%, – no statistically significant difference; Probability of being the best = 54%, 7 RCTs, n=534).
EVIDENCE OF HARMS	**Do the desirable effects outweigh the undesirable harms?** Favours intervention ☒ Favours control ☐ Intervention = Control *or* Uncertain ☐	
EASABILITY	**Is implementation of this recommendation feasible?** Yes ☒ No ☐ Uncertain ☐	

<table>
<tr><th></th><th>JUDGEMENT</th><th>EVIDENCE & ADDITIONAL CONSIDERATIONS</th></tr>
<tr><td>RESOURCE USE F</td><td>How large are the resource requirements?

More intensive: ☐ Less intensive: ☐ Uncertain: X</td><td>Cost of medicines/ year:

<table><tr><th>Medicine</th><th>Per patient</th><th>Budget impact</th></tr><tr><td></td><td colspan="2">Cost (ZAR) - SEP</td></tr><tr><td>infliximab</td><td>R10 370</td><td>R103 730</td></tr></table>
Cost of drug administration is more expensive however resources such as hospitalisation and surgery were not considered which are expected to offset costs.</td></tr>
<tr><td>VALUES, PREFERENCES, ACCEPTABILITY</td><td>Is there important uncertainty or variability about how much people value the options?

Minor: X Major: ☐ Uncertain: ☐

Is the option acceptable to key stakeholders?

Yes: X No: ☐ Uncertain: ☐</td><td></td></tr>
<tr><td>EQUITY</td><td>Would there be an impact on health inequity?

Yes: ☐ No: ☐ Uncertain: X</td><td></td></tr>
</table>

APPENDIX B – Search Strategy (Run 17 September 2024)

PUBMED

#	Query	Search Details	Results
#5	Meta-analyses, SRs	(("tumor necrosis factor inhibitors"[MeSH Terms] OR "infliximab"[MeSH Terms] OR "adalimumab"[MeSH Terms] OR "TNF inhibitors"[Title/Abstract] OR "golimumab"[Title/Abstract]) AND ("ulcerative colitis"[Title/Abstract] OR "colitis, ulcerative"[MeSH Terms])) AND (meta-analysis[Filter] OR systematicreview[Filter])	152
#4	RCTS, meta-analyses, SRs	(("tumor necrosis factor inhibitors"[MeSH Terms] OR "infliximab"[MeSH Terms] OR "adalimumab"[MeSH Terms] OR "TNF inhibitors"[Title/Abstract] OR "golimumab"[Title/Abstract]) AND ("ulcerative colitis"[Title/Abstract] OR "colitis, ulcerative"[MeSH Terms])) AND (meta-analysis[Filter] OR randomizedcontrolledtrial[Filter] OR systematicreview[Filter])	249
#3	#1 AND #2	("tumor necrosis factor inhibitors"[MeSH Terms] OR "infliximab"[MeSH Terms] OR "adalimumab"[MeSH Terms] OR "TNF inhibitors"[Title/Abstract] OR "golimumab"[Title/Abstract]) AND ("ulcerative colitis"[Title/Abstract] OR "colitis, ulcerative"[MeSH Terms])	2853
#2	Ulcerative colitis	"ulcerative colitis"[Title/Abstract] OR "colitis, ulcerative"[MeSH Terms]	63143
#1	Tumour necrosis factor inhibitors (adalimumab, infliximab, golimumab)	"tumor necrosis factor inhibitors"[MeSH Terms] OR "infliximab"[MeSH Terms] OR "adalimumab"[MeSH Terms] OR "TNF inhibitors"[Title/Abstract] OR "golimumab"[Title/Abstract]	21400

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search	**Query**	**Results**
#1	MeSH descriptor: [Colitis, Ulcerative] explode all trees	2269
#2	MeSH descriptor: [Tumor Necrosis Factor Inhibitors] explode all trees	170
#3	MeSH descriptor: [Adalimumab] explode all trees	1167
#4	MeSH descriptor: [Infliximab] explode all trees	1077
#5	golimumab	861
#6	#2 OR #3 OR #4 OR #5	3038
#7	#1 AND #6	207
#8	#7 in Cochrane reviews	8

APPENDIX C: LIST OF EXCLUDED STUDIES

Citation	Reason
Chang KH, Burke JP, Coffey JC. Infliximab versus cyclosporine as rescue therapy in acute severe steroid-refractory ulcerative colitis: a systematic review and meta-analysis. Int J Colorectal Dis. 2013 Mar;28(3):287-93. doi: 10.1007/s00384-012-1602-8. Epub 2012 Nov 1. PMID: 23114475.	Incorrect study design – SR of cohort studies
Choy MC, Seah D, Faleck DM, Shah SC, Chao CY, An YK, Radford-Smith G, Bessissow T, Dubinsky MC, Ford AC, Churilov L, Yeomans ND, De Cruz PP. Systematic Review and Meta-analysis: Optimal Salvage Therapy in Acute Severe Ulcerative Colitis. Inflamm Bowel Dis. 2019 Jun 18;25(7):1169-1186. doi: 10.1093/ibd/izy383. PMID: 30605549; PMCID: PMC6783899.	Incorrect study design – SR of cohort studies - Dosing study
Guo C, Wu K, Liang X, Liang Y, Li R. Infliximab clinically treating ulcerative colitis: A systematic review and meta-analysis. Pharmacol Res. 2019 Oct;148:104455. doi: 10.1016/j.phrs.2019.104455. Epub 2019 Sep 25. PMID: 31562896.	Incorrect population – not specifically severe acute
Jia X, Guo R, Hu Z, Liu J, Liu J, Li B, Yang Q, He J. Efficacy of infliximab, cyclosporine and tacrolimus on ulcerative colitis: A meta-analysis. Medicine (Baltimore). 2020 Oct 30;99(44):e22894. doi: 10.1097/MD.0000000000022894. PMID: 33126341; PMCID: PMC7598782.	Incorrect study design – SR of mixed studies including cohort studies
Komaki Y, Komaki F, Micic D, Yamada A, Suzuki Y, Sakuraba A. Pharmacologic therapies for severe steroid refractory hospitalized ulcerative colitis: A network meta-analysis. J Gastroenterol Hepatol. 2017 Jun;32(6):1143-1151. doi: 10.1111/jgh.13674. PMID: 27957761.	Full text availability
Lawson MM, Thomas AG, Akobeng AK. Tumour necrosis factor alpha blocking agents for induction of remission in ulcerative colitis. Cochrane Database Syst Rev. 2006 Jul 19;(3):CD005112. doi: 10.1002/14651858.CD005112.pub2. PMID: 16856078.	Incorrect population – not specifically acute and analysis of single dose for infliximab comprises one study which is included in Barberio 2021
Liu YJ, Fan H, Zhen WW, Yu X, Chen JT, Wang CD. Pooled analysis of the comparative efficacy between tacrolimus and infliximab for ulcerative colitis. Medicine (Baltimore). 2018 Aug;97(32):e11440. doi: 10.1097/MD.0000000000011440. PMID: 30095612; PMCID: PMC6133612.	Incorrect study design - SR of mixed studies with only 1 study for acute severe which was observational
Lv R, Qiao W, Wu Z, Wang Y, Dai S, Liu Q, Zheng X. Tumor necrosis factor alpha blocking agents as treatment for ulcerative colitis intolerant or refractory to conventional medical therapy: a meta-analysis. PLoS One. 2014 Jan 27;9(1):e86692. doi: 10.1371/journal.pone.0086692.	Incorrect population – not specifically acute and studies with single dose of infliximab excluded
Nalagatla N, Falloon K, Tran G, Borren NZ, Avalos D, Luther J, Colizzo F, Garber J, Khalili H, Melia J, Bohm M, Ananthakrishnan AN. Effect of Accelerated Infliximab Induction on Short- and Long-term Outcomes of Acute Severe Ulcerative Colitis: A Retrospective Multicenter Study and Meta-analysis. Clin Gastroenterol Hepatol. 2019 Feb;17(3):502-509.e1. doi: 10.1016/j.cgh.2018.06.031. Epub 2018 Jun 23.	Incorrect study design – retrospective study
Narula N, Marshall JK, Colombel JF, Leontiadis GI, Williams JG, Muqtadir Z, Reinisch W. Systematic Review and Meta-Analysis: Infliximab or Cyclosporine as Rescue Therapy in Patients With Severe Ulcerative Colitis Refractory to Steroids. Am J Gastroenterol. 2016 Apr;111(4):477-91. doi: 10.1038/ajg.2016.7. Epub 2016 Feb 9. PMID: 26856754.	Incorrect intervention, no placebo comparator
Thorne K, Alrubaiy L, Akbari A, Samuel DG, Morrison-Rees S, Roberts SE. Colectomy rates in patients with ulcerative colitis following treatment with infliximab or ciclosporin: a systematic literature review. Eur J Gastroenterol Hepatol. 2016 Apr;28(4):369-82. doi: 10.1097/MEG.0000000000000568. PMID: 26825217.	Incorrect study design - SR of mixed studies
Wang X, Li Q, Sun S, Liang X, Li H, Huang J, Zhao T, Hu J, Liu J, Hu Z, Duan Y, He J. Network meta-analysis and cost-effectiveness analysis of infliximab, cyclosporine and tacrolimus for ulcerative colitis. Medicine (Baltimore). 2022 Dec 23;101(51):e31850. doi: 10.1097/MD.0000000000031850.	Incorrect population, intervention
Wu D, Yang Z, Zhao C, Yao L. Infliximab versus cyclosporine for severe ulcerative colitis refractory to steroids: A protocol for systematic review and meta-analysis. Medicine (Baltimore). 2018 Oct;97(41):e12657. doi: 10.1097/MD.0000000000012657. PMID: 30313056; PMCID: PMC6203526.	Protocol, no study published
Zhao HN, Jiang M, Sun MJ, Dai C. The efficacy and safety of infliximab and calcineurin inhibitors in steroid-refractory UC patients: A meta-analysis. Saudi J Gastroenterol. 2021 Jul-Aug;27(4):191-200. doi: 10.4103/sjg.sjg_145_21. PMID: 34380865; PMCID: PMC8448007.	Not specific objective of review but subgroup by study type, however Barberio 2021 included same studies and more.

APPENDIX D –AMSTAR II Assessment

AMSTAR-2 item[11]	**Barberio 2021** **Low quality**
1. Did the research questions and inclusion criteria for the review include the components of PICO?	Yes
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	No
3. Did the review authors explain their selection of the study designs for inclusion in the review?	Yes
4. Did the review authors use a comprehensive literature search strategy?	Yes
5. Did the review authors perform study selection in duplicate?	Yes
6. Did the review authors perform data extraction in duplicate?	Yes
7. Did the review authors provide a list of excluded studies and justify the exclusions?	Partial Yes
8. Did the review authors describe the included studies in adequate detail?	Yes
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	Yes
10. Did the review authors report on the sources of funding for the studies included in the review?	No
11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?	Yes
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	Yes
13. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?	Yes
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	Yes
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	Yes
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes

APPENDIX E – SUMMARY AGREE II Assessments[iii]

AGREE II assessment scores																							
AGA GUIDANCE																							
Scoring the guidelines																							
	Scope and purpose			Stakeholder involvement			Rigour of development								Clarity of presentation			Applicability				Editorial independence		Overall assessment
	Item 1	Item 2	Item 3	Item 4	Item 5	Item 6	Item 7	Item 8	Item 9	Item 10	Item 11	Item 12	Item 13	Item 14	Item 15	Item 16	Item 17	Item 18	Item 19	Item 20	Item 21	Item 22	Item 23	Overall
Appraiser 1	7	7	7	4	6	4	6	6	6	4	6	7	7	7	7	5	6	1	2	6	1	6	5	123
Appraiser 2	6	6	6	5	6	6	6	6	6	6	6	6	7	7	6	6	6	5	5	2	5	5	6	131
Item Total	13	13	13	9	12	10	12	12	12	10	12	13	14	14	13	11	12	6	7	8	6	11	11	254
Domain Total	39			31			99								36			27				22		254
Minimum possible score	6			6			16								6			8				4		46
Maximum possible score	42			42			112								42			56				28		322
Domain score	92%			69%			**86%**								83%			40%				75%		**74%**

AGREE II assessment scores																							
ECCO 2022																							
Scoring the guidelines																							
	Scope and purpose			Stakeholder involvement			Rigour of development								Clarity of presentation			Applicability				Editorial independence		Overall assessment
	Item 1	Item 2	Item 3	Item 4	Item 5	Item 6	Item 7	Item 8	Item 9	Item 10	Item 11	Item 12	Item 13	Item 14	Item 15	Item 16	Item 17	Item 18	Item 19	Item 20	Item 21	Item 22	Item 23	Overall
Appraiser 1	6	6	5	5	6	3	6	5	6	6	5	6	2	2	6	6	6	2	2	2	2	5	6	106
Appraiser 2	6	5	6	6	7	5	5	6	6	6	6	6	6	2	6	6	6	5	3	1	3	5	7	120
Item Total	12	11	11	11	13	8	11	11	12	12	11	12	8	4	12	12	12	7	5	3	5	10	13	226
Domain Total	34			32			81								36			20				23		226
Minimum possible score	6			6			16								6			8				4		46
Maximum possible score	42			42			112								42			56				28		322
Domain score	78%			72%			**68%**								83%			25%				79%		**68%**

[iii] Acknowledgement: AGREE II results compiled into Excel© based format by KM initially developed by SA MRC

AGREE II assessment scores

PANCCO GUIDANCE

Scoring the guidelines

	Scope and purpose			Stakeholder involvement			Rigour of development								Clarity of presentation			Applicability				Editorial independence		Overall assessment
	Item 1	Item 2	Item 3	Item 4	Item 5	Item 6	Item 7	Item 8	Item 9	Item 10	Item 11	Item 12	Item 13	Item 14	Item 15	Item 16	Item 17	Item 18	Item 19	Item 20	Item 21	Item 22	Item 23	Overall
Appraiser 1	6	6	6	6	5	4	6	5	4	6	5	6	6	6	6	6	6	2	5	2	2	5	5	116
Appraiser 2	6	6	6	6	6	5	4	5	6	6	5	6	6	6	6	6	6	2	4	2	2	6	6	119
Item Total	12	12	12	12	11	9	10	10	10	12	10	12	12	12	12	12	12	4	9	4	4	11	11	235
Domain Total	36			32			88								36			21				22		235
Minimum possible score	6			6			16								6			8				4		46
Maximum possible score	42			42			112								42			56				28		322
Domain score	83%			72%			**75%**								83%			27%				75%		**69%**

AGREE II assessment scores

NICE GUIDANCE

Scoring the guidelines

	Scope and purpose			Stakeholder involvement			Rigour of development								Clarity of presentation			Applicability				Editorial independence		Overall assessment
	Item 1	Item 2	Item 3	Item 4	Item 5	Item 6	Item 7	Item 8	Item 9	Item 10	Item 11	Item 12	Item 13	Item 14	Item 15	Item 16	Item 17	Item 18	Item 19	Item 20	Item 21	Item 22	Item 23	Overall
Appraiser 1	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	138
Appraiser 2	5	5	6	6	7	7	7	7	6	6	6	5	5	4	6	5	4	2	7	6	4	7	6	129
Item Total	11	11	12	12	13	13	13	13	12	12	12	11	11	10	12	11	10	8	13	12	10	13	12	267
Domain Total	34			38			94								33			43				25		267
Minimum possible score	6			6			16								6			8				4		46
Maximum possible score	42			42			112								42			56				28		322
Domain score	78%			89%			**81%**								75%			73%				88%		**81%**

AGREE II assessment scores

Polish GUIDANCE

Scoring the guidelines

	Scope and purpose			Stakeholder involvement			Rigour of development								Clarity of presentation			Applicability				Editorial independence		Overall assessment
	Item 1	Item 2	Item 3	Item 4	Item 5	Item 6	Item 7	Item 8	Item 9	Item 10	Item 11	Item 12	Item 13	Item 14	Item 15	Item 16	Item 17	Item 18	Item 19	Item 20	Item 21	Item 22	Item 23	Overall
Appraiser 1	6	6	7	5	3	5	2	4	5	5	6	6	2	2	6	6	6	4	6	2	6	1	4	105
Appraiser 2	6	5	6	4	2	3	3	2	2	5	5	5	2	2	6	5	6	2	4	2	4	2	3	86
Item Total	12	11	13	9	5	8	5	6	7	10	11	11	4	4	12	11	12	6	10	4	10	3	7	191
Domain Total	36			22			58								35			30				10		191
Minimum possible score	6			6			16								6			8				4		46
Maximum possible score	42			42			112								42			56				28		322
Domain score	83%			44%			**44%**								81%			46%				25%		**54%**

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management of patients with Fistulising Crohn's Disease (PICO 1), who are refractory to conventional therapies. Medicine Review available from: https://knowledgehub.health.gov.za/system/files/elibdownloads/2024-04/Medicine%20Review_TNFi%20in%20CD_PICO%201_Fistulising%20CD_FINAL_April%202024.pdf

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