Appendix 2: Pediatric Crohn's disease, quality of evidence summaries

AMINOSALICYLATES

No consensus A

Evidence for No consensus A. In patients with mild Crohn's disease, the consensus group does not make a recommendation (for or against) regarding the use of 5-aminosalicylates to induce clinical remission.

PICO: In patients with mild Crohn's disease, should 5-aminosalicylates vs. placebo be used to induce clinical remission?

Statement 1

Evidence for statement 1: In patients with moderate Crohn's disease, we recommend against the use of 5-aminosalicylates to induce clinical remission.

PICO: In patients with moderate Crohn's disease, should 5-aminosalicylates vs. placebo be used to induce clinical remission?

Quality assessment								Summary of findings				Comments
								No of patients (ITT)		Effect		
Studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Quality of evidence	Overall quality of evidence	5ASA	Placebo	Relative (95% CI)	Absolute (95% CI)	
Failure to Achieve Clinical Remission (Induction): relative to placebo (follow up: 6-17 weeks) (**CRITICAL** for decision making)							⊕⊖⊖⊖ VERY LOW [f]					
2 SRs (4 RCTs)[1, 2] *Adult population*	Serious [a]	Not serious	Serious [b]	Very serious [c]	Potential publication bias [d]	⊕⊖⊖⊖ VERY LOW		313/437 (71.6%)	164/210 (78.1%)	RR 0.91 (0.77 to 1.06)	70 fewer per 1,000 (from 47 more to 180 fewer)	No statistically significant difference in clinical remission between 5ASA and placebo.
Adverse events: relative to placebo (follow up: 6-17 weeks) (**IMPORTANT** for decision making)												
2 SRs (4 RCTs)[1, 2] *Adult population*	Serious [a]	Not serious	Serious [b]	Very serious [e]	None	⊕⊖⊖⊖ VERY LOW		192/437 (43.9%)	95/210 (45.2%)	RR 0.99 (0.84 to 1.15)	5 fewer per 1,000 (from 68 more to 72 fewer)	No statistically significant difference in adverse events between 5ASA and placebo.

a. Most of the trials were unclear risk of bias for random sequence generation and allocation concealment.
b. Downgraded for indirectness. No pediatric data. Most trials included mild to moderate disease patients. Cannot separate mild from moderate disease.
c. Downgraded for imprecision as the 95% CI crosses the clinical decision threshold between recommending and not recommending 5ASA (i.e. clinical action would differ if the upper versus the lower boundary of the CI represented the truth). Results were borderline statistically significant, and became non-significant in sensitivity analyses.
d. One trial (Crohn's III), involving 310 patients, was never published. This trial showed no statistically significant difference in CDAI score between the 5ASA and placebo arms at the end of treatment.
e. Small sample size (n = 647) and low event rates (n = 287 adverse events). Optimal information size not met.
f. Overall quality of evidence is anchored on efficacy and safety data in adult population with no available pediatric data.

No consensus B

Evidence for No consensus B: In patients with mild Crohn's disease limited to the colon, the consensus group does not make a recommendation (for or against) regarding the use of sulfasalazine to induce clinical remission.

PICO: In patients with mild Crohn's disease, should sulfasalazine vs. placebo be used to induce clinical remission?

Statement 2

Evidence for statement 2: In patients with moderate Crohn's disease limited to the colon, we suggest against the use of sulfasalazine to induce clinical remission.

PICO: In patients with moderate Crohn's disease, should sulfasalazine vs. placebo be used to induce clinical remission?

Quality assessment								Summary of findings				Comments
								No of patients (Per Protocol)		Effect		
Studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Quality of evidence	Overall quality of evidence	Sulfasalazine	Placebo	Relative (95% CI)	Absolute (95% CI)	
Clinical Remission (Induction): relative to placebo (follow up: 6-17 weeks) (**CRITICAL** for decision making)							⊕⊖⊖⊖ **VERY LOW** [e]					
2 SRs (2 RCTs)[1, 2] *Adult population*	Serious [a]	Not serious	Serious [b]	Very serious [c]	None	⊕⊖⊖⊖ **VERY LOW**		55/128 (43.0%)	42/135 (31.1%)	RR 1.38 (1.00 to 1.89)	118 more per 1,000 (from 0 fewer to 277 more)	Marginal benefit of sulfasalazine over placebo for induction of clinical remission.
Adverse events: relative to placebo (follow up: 6-17 weeks) (**IMPORTANT** for decision making)												
2 SRs (1 RCTs)[1, 2] *Adult population*	Serious [a]	Not serious	Serious [b]	Very serious [d]	None	⊕⊖⊖⊖ **VERY LOW**		10/74 (13.5%)	5/77 (6.5%)	RR 2.08 (0.75 to 5.80)	70 more per 1,000 (from 16 fewer to 312 more)	No statistically significant difference in adverse events between sulfasalazine and placebo.

a. Both trials were unclear risk of bias for random sequence generation and one had unclear method of allocation concealment.
b. Downgraded for indirectness. No pediatric data. Both trials included mild to moderate disease patients. Cannot separate mild from moderate disease, or colonic disease from non-colonic disease.
c. Downgraded for imprecision as the 95% CI crosses the clinical decision threshold between recommending and not recommending sulfasalazine (i.e. clinical action would differ if the upper versus the lower boundary of the CI represented the truth). Both trials included very small number of patients with active or quiescent colonic only disease (n = 67). Both trials found statistically significant benefit for colonic disease, but not for ileal or ileocolonic disease. Small sample size (n = 263) and low event rates (n = 97 clinical remission). Optimal information size not met.
d. Downgraded for imprecision as the 95% CI crosses the clinical decision threshold between recommending and not recommending sulfasalazine (i.e. clinical action would differ if the upper versus the lower boundary of the CI represented the truth). Small sample size (n = 151) and low event rates (n = 15 adverse events). Optimal information size not met.
e. Overall quality of evidence is anchored on efficacy and safety data in adult population with no available pediatric data.

No consensus C

Evidence for No consensus C: In patients with mild Crohn's disease who have achieved clinical remission with sulfasalazine or 5-aminosalicylic acid, the consensus group does not make a recommendation (for or against) regarding continuing sulfasalazine or 5-aminosalicylic acid to maintain clinical remission.

PICO: In patients with mild Crohn's disease who have achieved clinical remission with sulfasalazine or 5-aminosalicylic acid, should sulfasalazine or 5-aminosalicylic acid vs. placebo be used to maintain clinical remission?

Statement 3

Evidence for statement 3: In patients with Crohn's disease in clinical remission, we recommend against sulfasalazine or 5-aminosalicylic acid to maintain clinical remission.

PICO: In patients with Crohn's disease in clinical remission, should sulfasalazine or 5-aminosalicylic acid vs. placebo be used to maintain clinical remission?

Quality assessment								Summary of findings				Comments
								No of patients (ITT)		Effect		
Studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Quality of evidence	Overall quality of evidence	Sulfasalazine or 5-aminosalicylic acid	Placebo	Relative (95% CI)	Absolute (95% CI)	
Relapse (Maintenance): relative to placebo (follow up: 6-48 months) (**CRITICAL** for decision making)							⊕⊖⊖⊖ VERY LOW [l]					
2 SRs (16 RCTs)[1, 3] *Adult population*	Serious [a]	Not serious	Serious [b]	Very serious [c]	None	⊕⊖⊖⊖ VERY LOW		682/1222 (55.8%)	726/1274 (57.0%)	RR 0.97 (0.90 to 1.05)	17 fewer per 1,000 (from 28 more to 57 fewer)	No statistically significant difference in relapse between sulfasalazine or mesalamine and placebo.
Relapse (Maintenance): relative to placebo (follow up: 12 months) (**CRITICAL** for decision making)												
1 RCT[4] *Pediatric population*	Serious [d]	Not serious	Not serious	Very serious [e]	None	⊕⊖⊖⊖ VERY LOW		50/68 (73.5%)	44/64 (68.8%)	RR 1.07 (0.86 to 1.33)	48 more per 1,000 (from 96 fewer to 227 more)	No statistically significant difference in relapse between mesalamine and placebo.
Adverse events: relative to placebo (follow up: 6-24 months) (**IMPORTANT** for decision making)												
SRs (12 RCTs)[1, 3] *Adult population*	Serious [a]	Not serious	Serious [f]	Very serious [g]	None	⊕⊖⊖⊖ VERY LOW		217/987 (22.0%)	202/1007 (20.1%)	RR 1.08 (0.87 to 1.34)	16 more per 1,000 (from 26 fewer to 68 more)	No statistically significant difference in adverse events between sulfasalazine or mesalamine and placebo.
Adverse events: relative to placebo (follow up: 12 months) (**IMPORTANT** for decision making)												
1 RCT[4] *Pediatric population*	Serious [d]	Not serious	Not serious	Very serious [h]	None	⊕⊖⊖⊖ VERY LOW		32/68 (47.1%)	29/64 (45.3%)	RR 1.04 (0.72 to 1.50)	18 more per 1,000 (from 127 fewer to 227 more)	No statistically significant difference in adverse events between mesalamine and placebo.

a. Most of the trials were unclear risk of bias for random sequence generation and allocation concealment. One trial was high risk of bias for random sequence generation and allocation concealment.

b. The systematic review by Ford et al[1] included 16 RCTs (all adult data) with 4 comparing sulfasalazine vs. placebo and 12 comparing mesalamine vs. placebo. A more recent systematic review by Akobeng et al[3] included 12 RCTs comparing mesalamine vs. placebo (only one pediatric RCT), and excluded the 4 RCTs included by Ford et al[3] that compared sulfasalazine vs. placebo. Also, patients were induced into clinical remission by different medications (not necessarily sulfasalazine or mesalamine) before entering the maintenance studies.
c. Downgraded for imprecision as the 95% CI crosses the clinical decision threshold between recommending and not recommending sulfasalazine or mesalamine (i.e. clinical action would differ if the upper versus the lower boundary of the CI represented the truth). Only 4 small trials on sulfasalazine.
d. Unclear risk of bias for random sequence generation and allocation concealment.
e. Downgraded for imprecision as the 95% CI crosses the clinical decision threshold between recommending and not recommending mesalamine (i.e. clinical action would differ if the upper versus the lower boundary of the CI represented the truth). Small sample size (n = 132) and low event rates (n = 94 relapse). Optimal information size not met
f. The systematic review by Ford et al[1] included 12 RCTs (all adult data) that reported adverse events. A more recent systematic review by Akobeng et al[3] included 10 RCTs that reported adverse events (only one pediatric RCT).
g. Downgraded for imprecision as the 95% CI crosses the clinical decision threshold between recommending and not recommending sulfasalazine or mesalamine (i.e. clinical action would differ if the upper versus the lower boundary of the CI represented the truth). Only 1 small trial on sulfasalazine reported adverse events. Small sample size (n = 43) and low event rates (n = 8 adverse events). Optimal information size not met.
h. Downgraded for imprecision as the 95% CI crosses the clinical decision threshold between recommending and not recommending mesalamine (i.e. clinical action would differ if the upper versus the lower boundary of the CI represented the truth). Small sample size (n = 132) and low event rates (n = 61 adverse events). Optimal information size not met.
i. Overall quality of evidence is anchored on efficacy and safety data in adult population with support of pediatric data.

ANTIBIOTICS

No consensus D

Evidence for No consensus D. In patients with mild to moderate Crohn's disease, the consensus group does not make a recommendation (for or against) regarding the use of antibiotics to induce clinical remission.

PICO: In patients with mild to moderate Crohn's disease, should antibiotics vs. placebo be used to induce clinical remission?

Quality assessment								Summary of findings				Comments
								No of patients (ITT)		Effect		
Studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Quality of evidence	Overall quality of evidence	Antibiotics	Placebo	Relative (95% CI)	Absolute (95% CI)	
Failure to Achieve Clinical Remission (Induction): relative to placebo (follow up: 4-16 weeks) (**CRITICAL** for decision making)							⊕⊖⊖⊖ **VERY LOW**[i]					
2 SRs (10 RCTs)[5, 6] *Adult population*	Serious[a]	Not serious[b]	Serious[c]	Serious[d]	None	⊕⊖⊖⊖ **VERY LOW**		347/702 (49.4%)	275/458 (60.0%)	**RR 0.85 (0.73 to 0.99)**	**90 fewer per 1,000 (from 6 fewer to 162 fewer)**	Antibiotics is superior to placebo for induction of clinical remission. However, the results became non-significant when the 2 rifaximin trials were removed.
Serious adverse events: **relative to placebo** (follow up: 16 weeks) (**IMPORTANT** for decision making)												
2 RCTs[7, 8] *Adult population*	Serious[e]	Not serious[f]	Serious[g]	Serious[h]	None	⊕⊖⊖⊖ **VERY LOW**		27/353 (7.6%)	17/128 (13.3%)	RR 0.74 (0.48 to 1.14)	35 fewer per 1,000 (from 19 more to 69 fewer)	Both trials were on rifaximin. The above SRs did not provide data on adverse events for all antibiotics.

a. Most of the trials were unclear risk of bias for random sequence generation and allocation concealment. Only 1 RCT was considered low risk of bias overall.
b. There was moderate heterogeneity (I^2 = 44%) for all antibiotics. But there was little heterogeneity for any given antibiotic.

c. Downgraded for indirectness. No pediatric data. Diverse regimens were used and conclusions could not be drawn for any specific antibiotic. Patient characteristics were diverse and results were not reported separately according to the location or extent of the disease.
d. Downgraded for imprecision as the 95% CI crosses the clinical decision threshold between recommending and not recommending antibiotics (i.e. clinical action would differ if the upper versus the lower boundary of the CI represented the truth).
e. Both trials were unclear risk of bias for random sequence generation and allocation concealment.
f. No significant heterogeneity (I^2 = 16%) when both trials were pooled.
g. Downgraded for indirectness. No pediatric data.
h. Downgraded for imprecision as the 95% CI crosses the clinical decision threshold between recommending and not recommending rifaximin (i.e. clinical action would differ if the upper versus the lower boundary of the CI represented the truth). Small sample size (n = 481) and low event rates (n = 44). Optimal information size not met.
i. Overall quality of evidence is anchored on efficacy and safety data in adult population with no available pediatric data.

No consensus E

Evidence for No consensus E. In patients with mild to moderate Crohn's disease, the consensus group does not make a recommendation (for or against) regarding the use of antibiotics to maintain clinical remission.

PICO: In patients with mild to moderate Crohn's disease, should antibiotics vs. placebo be used to maintain clinical remission?

Quality assessment								Summary of findings				
								No of patients (ITT)		Effect		
Studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Quality of evidence	Overall quality of evidence	Antibiotics	Placebo	Relative (95% CI)	Absolute (95% CI)	Comments
Relapse (Maintenance): relative to placebo (follow up: 9-12 months) (**CRITICAL** for decision making)												
2 SRs (4 RCTs)[5, 9] *Adult population*	Serious [a]	Not serious	Serious [b]	Serious [c]	None	⊕⊖⊖⊖ **VERY LOW**	⊕⊖⊖⊖ **VERY LOW** [i]	44/112 (39.3%) Anti-mycobacterial regimens	63/94 (67.0%)	**RR 0.58 (0.45 to 0.75)**	**281 fewer per 1,000 (from 168 fewer to 369 fewer)**	Antibiotics (anti-mycobacterial regimens) is superior to placebo in preventing relapse.
Clinical remission: relative to placebo (follow up: 48 weeks) (**CRITICAL** for decision making)												
1 RCT[10] *Adult population*	Very Serious [d]	Not serious	Serious [e]	Serious [f]	None	⊕⊖⊖⊖ **VERY LOW**		59/84 (70.2%) Rifaximin	44/84 (52.4%)	**RR 1.34 (1.05 to 1.72)**	**178 more per 1,000 (from 26 more to 377 more)**	Rifaximin 800mg daily is superior to placebo for maintenance of clinical remission.
Adverse events: relative to placebo (follow up: 9 – 12 months) (**IMPORTANT** for decision making)												
2 SRs (4 RCTs)[5, 9] *Adult population*	Serious [a]	Serious [g]	Serious [b]	Serious [h]	None	⊕⊖⊖⊖ **VERY LOW**		37/159 (23.3%) Anti-mycobacterial regimens	14/163 (8.6%)	**RR 2.57 (1.45 to 4.55)**	**135 more per 1,000 (from 39 more to 305 more)**	Significantly more adverse events with antibiotics (anti-mycobacterial regimens) than with placebo.

a. Most trials were unclear risk of bias for random sequence generation and all trials were unclear risk of bias for allocation concealment. Two trials were unclear risk of bias for blinding.
b. Downgraded for indirectness. No pediatric data. Variability in patient populations, antibiotic regimens (all could be considered anti-mycobacterial), and definitions of relapse.
c. Small sample size (n = 206) and low event rates (n = 107 relapse). Optimal information size not met.
d. Unclear risk of bias for random sequence generation. No mention of randomization in the full text.
e. Downgraded for indirectness. No pediatric data. Variability in concurrent medications for maintenance. Unclear how patients were induced into remission. Lack of description of baseline characteristics of patients.

f. Small sample size (n = 168) with low event rates (n = 103 clinical remission). Optimal information size not met.
g. Statistically significant heterogeneity (I^2 = 64%).
h. Small sample size (n = 322) and low event rates (n = 51 adverse events). Optimal information size not met.
i. Overall quality of evidence is anchored on efficacy and safety data in adult population with no available pediatric data.

BUDESONIDE

Statement #4

Evidence for statement #4: In patients with mild to moderate ileal and/or right colonic Crohn's disease, we suggest oral controlled ileal-release budesonide to induce clinical remission.

PICO: In patients with mild to moderate ileal and/or right colonic Crohn's disease, should oral controlled ileal-release budesonide vs. placebo or conventional corticosteroids be used to induce clinical remission?

Statement #7

Evidence for statement #7: In patients with mild to moderate active Crohn's disease despite use of sulfasalazine, 5-aminosalicylate, oral budesonide, or exclusive enteral nutrition we suggest oral prednisolone to induce clinical remission.

PICO: In patients with mild to moderate active Crohn's disease despite use of sulfasalazine, 5-aminosalicylate, oral budesonide, or exclusive enteral nutrition, should conventional corticosteroids vs. placebo be used to induce clinical remission?

Quality assessment								Summary of findings				Comments
								No of patients (ITT)		Effect		
Studies	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Quality of evidence**	**Overall quality of evidence**	**Oral controlled ileal-release budesonide (9mg daily)**	**Comparator**	**Relative (95% CI)**	**Absolute (95% CI)**	
Clinical Remission (Induction): relative to placebo (follow up: 8 weeks) (**CRITICAL** for decision making)							⊕⊕⊖⊖ **LOW** [J]					
4 SRs (3 RCTs)[11-14] *Adult population*	Serious [a]	Not serious	Serious [b]	Serious [c]	None	⊕⊖⊖⊖ **VERY LOW**		115/246 (46.7%)	29/133 (21.8%) Placebo	**RR 1.93 (1.37 to 2.73)**	**203 more per 1,000 (from 81 more to 377 more)**	Budesonide 9mg daily is superior to placebo for induction of clinical remission.
Clinical Remission (Induction): relative to conventional steroids (follow up: 8 weeks) (**CRITICAL** for decision making)												
4 SRs (8 RCTS)[11-14] *Adult population*	Serious [a]	Not serious	Serious [b]	Not serious	None	⊕⊕⊖⊖ **LOW**		211/406 (52.0%)	210/344 (61.0%) conventional steroids	**RR 0.85 (0.75 to 0.97)**	**92 fewer per 1,000 (from 18 fewer to 153 fewer)**	Budesonide 9mg daily is significantly less effective than conventional steroids for induction of clinical remission.
Clinical Remission (Induction): relative to conventional steroids (follow up: 8–12 weeks) (**CRITICAL** for decision making)												
2 RCTs[15, 16] *Pediatric population*	Serious [d]	Not serious	Not serious	Serious [e]	None	⊕⊕⊖⊖ **LOW**		21/41 (51.2%)	24/40 (60.0%) conventional steroids	RR 1.68 (0.68 to 4.15)	408 more per 1,000 (from 192 fewer to 1,000 more)	No significant difference between Budesonide 9mg daily and conventional steroids for induction of clinical remission.
Adverse events: relative to placebo (follow up: 8 weeks) (**IMPORTANT** for decision making)												

4 SRs (3 RCTs)[11-13] *Adult population*	Serious [a]	Not serious	Serious [b]	Serious [f]	None	⊕⊖⊖⊖ **VERY LOW**		115/251 (45.8%)	44/133 (33.1%) Placebo	RR 0.97 (0.76 to 1.23)	10 fewer per 1,000 (from 76 more to 79 fewer)	No significant difference between Budesonide 9 mg daily and placebo for corticosteroid related adverse events.
Adverse events: relative to conventional steroids (follow up: 8 weeks) (**IMPORTANT** for decision making)												
4 SRs (6 RCTs)[11-14] *Adult population*	Serious [a]	Not serious	Serious [b]	Not serious	None	⊕⊕⊖⊖ **LOW**		156/383 (40.7%)	203/320 (63.4%) conventional steroids	**RR 0.64 (0.54 to 0.76)**	**228 fewer per 1,000 (from 152 fewer to 292 fewer)**	Significantly fewer corticosteroid-related adverse events with Budesonide 9mg daily than with conventional steroids.
Adverse events (follow up: 8 weeks) (**IMPORTANT** for decision making)												
1 Observational study[17] *Pediatric population*	Very serious [g]	Not serious	Not serious	Very serious [h]	None	⊕⊖⊖⊖ **VERY LOW**		79/108 (73.1%)	-	-	-	Pediatric case series of budesonide for induction and maintenance of remission of Crohn's disease. Most adverse events were minor.
Adverse events: relative to conventional steroids (follow up: 8–12 weeks) (**IMPORTANT** for decision making)												
2 RCTs[15, 16] *Pediatric population*	Serious [d]	Not serious	Not serious	Serious [i]	None	⊕⊕⊖⊖ **LOW**		17/41 (41.5%)	30/40 (75.0%) conventional steroids	**RR 0.25 (0.10 to 0.64)**	**563 fewer per 1,000 (from 270 fewer to 675 fewer)**	Significantly fewer corticosteroid-related adverse events with Budesonide 9mg daily than with conventional steroids.

a. Most of the trials were unclear risk of bias for allocation concealment.
b. No pediatric data.
c. Small sample size (n = 379) and low event rates (n = 144 clinical remission). Optimal information size not met.
d. Both trials were stopped prematurely due to low enrollment. One trial was unblinded. High withdrawal rates in one trial.
e. Small sample size (n = 81) and low event rates (n = 38 clinical remission). Optimal information size not met.
f. Small sample size (n = 384) and low event rates (n = 159 adverse events). Optimal information size not met.
g. Uncontrolled and open label design. High risk for selection, performance and detection bias.
h. Small sample size (n = 108) and low event rates (n = 79 adverse events). Optimal information size not met.
i. Small sample size (n = 81) and low event rates (n = 27 adverse events). Optimal information size not met.
j. Overall quality of evidence is anchored on efficacy and safety data in adult population with support of pediatric data.

Statement #5

Evidence for statement #5: In patients with Crohn's disease, we recommend <u>against</u> oral controlled ileal-release budesonide to maintain clinical remission.

PICO: In patients with Crohn's disease, should oral controlled ileal-release budesonide vs. placebo be used to maintain clinical remission?

Quality assessment								Summary of findings				
								No of patients (ITT)		Effect		
Studies	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Quality of evidence**	**Overall quality of evidence**	**Oral controlled ileal-release budesonide (6mg daily)**	**Placebo**	**Relative (95% CI)**	**Absolute (95% CI)**	**Comments**
Clinical Remission (Maintenance): relative to placebo (follow up: 12 months) (**CRITICAL** for decision making)												
4 SRs (5 RCTs)[12, 13, 18, 19]	Serious [a]	Not serious	Serious [b]	Serious [c]	None	⊕⊖⊖⊖ **VERY LOW**	⊕⊖⊖⊖ **VERY LOW** [g]	114/208 (54.8%)	101/212 (47.6%)	RR 1.13 (0.94 to 1.35)	62 more per 1,000	No statistically significant difference in clinical remission between

Adult population											(from 29 fewer to 167 more)	Budesonide 6mg daily and placebo.
Adverse events: relative to placebo (follow up: 12 months) (**IMPORTANT** for decision making)												
4 SRs (5 RCTs)[12, 13, 18, 19] *Adult population*	Serious [a]	Not serious	Serious [b]	Serious [d]	None	⊕⊖⊖⊖ **VERY LOW**		111/208 (53.4%)	96/186 (51.6%)	**RR 2.19 (1.08 to 4.46)**	**614 more per 1,000 (from 41 more to 1000 more) NNH = 6 (4 to 25)**	Significantly higher risk of adverse events with Budesonide 6mg daily compared to placebo. Most adverse events were minor: acne, moon facies, hirsutism, mood.swings, insomnia, weight gain, striae, and hair loss.
Adverse events (follow up: 20 weeks) (**IMPORTANT** for decision making)												
1 Observational study[17] *Pediatric population*	Very serious [e]	Not serious	Not serious	Very serious [f]	None	⊕⊖⊖⊖ **VERY LOW**		37/50 (74.0%)	-	-	-	Pediatric case series of budesonide for induction and maintenance of remission of Crohn's disease. Most adverse events were minor.

a. Most of the trials were unclear risk of bias for allocation concealment.
b. Downgraded for indirectness. No pediatric data on efficacy.
c. Downgraded for imprecision as the 95% CI crosses the clinical decision threshold between recommending and not recommending budesonide (i.e. clinical action would differ if the upper versus the lower boundary of the CI represented the truth). Small sample size (n = 420) and low even rates (n = 215 clinical remission). Optimal information size not met.
d. Small sample size (n = 419) and low event rates (n = 87 adverse events). Optimal information size not met.
e. Uncontrolled and open label design. High risk for selection, performance and detection bias.
f. Small sample size (n = 50) and low event rates (n = 37)
g. Overall quality of evidence is anchored on efficacy and safety data in adult population with no available pediatric data on efficacy.

CORTICOSTEROIDS

Statement #6

Evidence for statement #6: In patients with moderate to severe Crohn's disease, we suggest conventional corticosteroids (e.g. prednisone) to induce clinical remission.

PICO: In patients with moderate to severe Crohn's disease, should conventional corticosteroids vs. placebo be used to induce clinical remission?

Statement #7

Evidence for statement #7: In patients with mild to moderate active Crohn's disease despite use of sulfasalazine, 5-aminosalicylate, oral budesonide, or exclusive enteral nutrition, we suggest oral prednisolone to induce clinical remission.

PICO: In patients with mild to moderate active Crohn's disease despite use of sulfasalazine, 5-aminosalicylate, oral budesonide, or exclusive enteral nutrition, should conventional corticosteroids vs. placebo be used to induce clinical remission?

Quality assessment								Summary of findings				Comments
Studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Quality of evidence	Overall quality of evidence	No of patients (ITT)		Effect		
								Conventional corticosteroids	Comparator	Relative (95% CI)	Absolute (95% CI)	
Clinical Remission (Induction): relative to placebo (follow up: 15+ weeks) (**CRITICAL** for decision making)												
2 SRs (2 RCTs)[12, 20] *Adult population*	Serious [a]	Not serious	Serious [b]	Serious [c]	None	⊕⊖⊖⊖ **VERY LOW**		79/132 (59.8%)	42/135 (31.1%) Placebo	**RR 1.99 (1.51 to 2.64)**	**308 more per 1,000 (from 159 more to 510 more)**	Conventional corticosteroids is superior to placebo for induction of clinical remission.
Clinical Remission (Induction): relative to EEN (follow up: 10 weeks) (**CRITICA**L for decision making)												
1 RCT [21] *Pediatric population*	Serious [d]	Not serious	Serious [e]	Very Serious [f]	None	⊕⊖⊖⊖ **VERY LOW**	⊕⊖⊖⊖ **VERY LOW** [h]	12/18 (66.7%)	15/19 (78.9%) Exclusive enteral nutrition	RR 1.18 (0.79 to 1.77)	142 more per 1,000 (from 166 fewer to 608 more)	No statistically significant difference in clinical remission between corticosteroids and exclusive enteral nutrition.
Adverse events: relative to placebo (follow up: 15+ weeks) (**IMPORTANT** for decision making)												
2 SRs (2 RCTs)[12, 20] *Adult population*	Serious [a]	Not serious	Serious [b]	Very Serious [g]	None	⊕⊖⊖⊖ **VERY LOW**		27/85 (31.8%)	5/77 (6.5%) Placebo	**RR 4.89 (1.98 to 12.07)**	**253 more per 1,000 (from 64 more to 719 more)**	Significantly more adverse events with conventional corticosteroids than with placebo.

a. Both trials were unclear risk of bias for random sequence generation, and one trial was unclear risk of bias for allocation concealment.
b. No placebo controlled pediatric data.
c. Small sample size (n = 267) and low event rates (n = 60 clinical remission). Optimal information size not met.
d. Unblinded study and primary outcome has subjective elements.
e. Pediatric population, but not comparing with placebo and not specifically in moderate or severe Crohn's disease.
f. Downgraded for imprecision as the 95% CI crosses the clinical decision threshold between recommending and not recommending conventional corticosteroids (i.e. clinical action would differ if the upper versus the lower boundary of the CI represented the truth). Small sample size (n = 37) and low event rates (n = 27 clinical remission). Optimal information size not met.
g. Small sample size (n = 162) and low event rates (n = 32 adverse events). Optimal information size not met.
h. Overall quality of evidence is anchored on efficacy and safety data in adult population. Lack of placebo controlled pediatric data.

Statement #8

Evidence for statement #8: In patients with Crohn's disease of any severity, we recommend <u>against</u> oral corticosteroids to maintain clinical remission.

PICO: In patients with Crohn's disease of any severity, should conventional corticosteroids vs. placebo be used to maintain clinical remission?

Quality assessment								Summary of findings				Comments
Studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Quality of evidence	Overall quality of evidence	No of patients (ITT)		Effect		
								Conventional corticosteroids	Placebo	Relative (95% CI)	Absolute (95% CI)	
Relapse (Maintenance): relative to placebo (follow up: 12 months) (**CRITICAL** for decision making)												

1 SRs (3 RCTs)[22] *Adult population*	Serious [a]	Not serious	Not serious [b]	Serious [c]	None	⊕⊕⊖⊖ **LOW**	⊕⊕⊖⊖ **LOW** [d]	37/131 (28.2%)	43/138 (31.2%)	OR 0.82 (0.47 to 1.44)	41 fewer per 1,000 (from 83 more to 136 fewer)	No statistically significant difference in relapse between conventional corticosteroids and placebo.
Adverse events: relative to placebo (follow up: 12 months) (**IMPORTANT** for decision making)												
1 SRs (3 RCTs)[22] *Adult population*	Adequate safety data were not available in the included studies to allow comparison of adverse event rates in patients receiving corticosteroids vs. placebo.											

a. Two of the three trials did not state method of concealment. High attrition (only 36% of patients available for the 12-month analysis)
b. One trial did enroll some children and gave similar results
c. Downgraded for imprecision as the 95% CI crosses the clinical decision threshold between recommending and not recommending conventional corticosteroids (i.e. clinical action would differ if the upper versus the lower boundary of the CI represented the truth). Small sample size (n = 269) and low event rates (n = 80 relapse). Optimal information size not met.
d. Overall quality of evidence is anchored on efficacy and safety data in adult population with support of pediatric data.

EXCLUSIVE ENTERAL NUTRITION

Statement #9

Evidence for statement #9: In patients with Crohn's disease, we suggest exclusive enteral nutrition to induce clinical remission.

PICO: In patients with Crohn's disease, should exclusive enteral nutrition (EEN) vs. placebo or other treatments (e.g. corticosteroids, 5-aminosalicylates, immunosuppressives, biologics) be used to induce clinical remission?

Quality assessment								Summary of findings				Comments
								No of patients (ITT)		Effect		
Studies	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Quality of evidence**	**Overall quality of evidence**	**EEN**	**Steroids**	**Relative (95% CI)**	**Absolute (95% CI)**	
Clinical Remission (Induction): relative to steroids (follow up: 4-10 weeks) (**CRITICAL** for decision making)							⊕⊖⊖⊖ **VERY LOW** [j]					
1 SR (9 RCTs)[21, 23-29] *Mixed Adult and Pediatric population*	Serious [a]	Serious [b]	Serious [c]	Serious [d]	None	⊕⊖⊖⊖ **VERY LOW**		123/235 (52.3%)	150/200 (75.0%)	**OR 0.43 (0.22 to 0.87)**	**438 fewer per 1,000 (from 98 fewer to 585 fewer)**	EEN was inferior to corticosteroids for achieving clinical remission.
2 RCTs[21, 23] *Pediatric population*	Serious [e]	Not serious	Not serious	Very serious [f]	None	⊕⊖⊖⊖ **VERY LOW**		24/29 (82.8%)	17/28 (60.7%)	OR 3.04 (0.73 to 12.65)	1,000 more per 1,000 (from 164 fewer to 1,000 more)	No statistically significant difference in clinical remission between EEN and corticosteroids.
Adverse events: relative to steroids (follow up: 4-10 weeks) (IMPORTANT) for decision making)												
1 SR (4 RCTs)[21, 24, 25, 27] *Overall*	Serious [a]	Serious [g]	Serious [h]	Serious [i]	None	⊕⊖⊖⊖ **VERY LOW**		27/130 (20.8%)	31/103 (30.1%)	OR 0.41 (0.15 to 1.09)	178 fewer per 1,000 (from 27 more to 256 fewer)	No statistically significant difference in the incidence of adverse events between EEN and corticosteroids.

a. Most trials had unclear risk of bias for allocation concealment and randomization, lack of blinding, and incomplete outcome data with high withdrawal rates, particularly in the EEN arms (24% in EEN group vs. 6% in steroids group).

b. Unexplained statistical heterogeneity (I^2 = 52%)
c. Downgraded for indirectness. Although 2 of the 7 trials were pediatric studies, there was wide variation in disease activity, onset of disease and disease location in recruited subjects. There were also variations in study design, types of enteral formula used, the types of scoring systems used to define disease activity and remission, the duration of interventions, the length of follow-up, and the use of concomitant medications.
d. Small sample size (n = 435) and low event rates (n = 162 for relapse). Optimal information size not met.
e. Both trials had unclear risk of bias for allocation concealment, lack of blinding, and incomplete outcome data (14% withdrawal rate) in one trial.
f. Downgraded for imprecision as the 95% CI crosses the clinical decision threshold between recommending and not recommending EEN (i.e. clinical action would differ if the upper versus the lower boundary of the CI represented the truth).
g. Unexplained statistical heterogeneity (I^2 = 46%)
h. Downgraded for indirectness. Although one of the 4 trials was a pediatric study, there was wide variation in disease activity, onset of disease and disease location in recruited subjects. There were also variations in study design, types of enteral formula used, the types of scoring systems used to define disease activity and remission, the duration of interventions, the length of follow-up, and the use of concomitant medications.
i. Small sample size (n = 233) and low event rates (n = 58). Optimal information size not met.
j. Overall quality of evidence is anchored on efficacy and safety data in adult population. Available pediatric data may or may not support adult data.

Statement #10

Evidence for statement #10: In patients with Crohn's disease, we recommend <u>against</u> partial enteral nutrition to induce clinical remission.

PICO: In patients with Crohn's disease, should partial enteral nutrition (PEN) vs. placebo or other treatments (e.g. corticosteroids, 5-aminosalicylates, immunosuppressives, biologics) be used to induce clinical remission?

Quality assessment								Summary of findings				Comments
								No of patients (ITT)		Effect		
Studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Quality of evidence	Overall quality of evidence	EN	Comparator	Relative (95% CI)	Absolute (95% CI)	
Clinical Remission (Induction): relative to steroids / EEN (follow up: 4-10 weeks) (**CRITICAL** for decision making)							⊕⊖⊖⊖ **VERY LOW** [j]					
1 SR (9 RCTs) [21, 23-29] *Mixed Adult and Pediatric population*	Serious [a]	Serious [b]	Very serious [c]	Serious [d]	None	⊕⊖⊖⊖ **VERY LOW**		123/235 (52.3%) EEN	150/200 (75.0%) Steroids	**OR 0.43 (0.22 to 0.87)**	**438 fewer per 1,000 (from 98 fewer to 585 fewer)**	EEN was inferior to corticosteroids for achieving clinical remission.
1 RCT[30] *Pediatric population*	Serious [e]	Not serious	Serious [f]	Very serious [g]	None	⊕⊖⊖⊖ **VERY LOW**		4/26 (15.4%) PEN	10/24 (41.7%) EEN	**OR 0.25 (0.07 to 0.97)**	**265 fewer per 1,000 (from 7 fewer to 369 fewer)**	PEN was inferior to EEN for achieving clinical remission.
Adverse events: relative to steroids (follow up: 4-10 weeks) (IMPORTANT) for decision making)												
1 SR (4 RCTs)[21, 24, 25, 27] *Overall*	Serious [a]	Serious [h]	Serious [c]	Serious [i]	None	⊕⊖⊖⊖ **VERY LOW**		27/130 (20.8%) EEN	31/103 (30.1%) Steroids	OR 0.41 (0.15 to 1.09)	178 fewer per 1,000 (from 27 more to 256 fewer)	No statistically significant difference in the incidence of adverse events between EEN and corticosteroids.

a. Most trials had unclear risk of bias for allocation concealment and randomization, lack of blinding, and incomplete outcome data with high withdrawal rates, particularly in the EEN arms (24% in EEN group vs. 6% in steroids group).
b. Unexplained statistical heterogeneity (I^2 = 52%)
c. Downgraded for indirectness. Although 2 of the 7 trials were pediatric studies, there was wide variation in disease activity, onset of disease and disease location in recruited subjects. There were also variations in study design, types of enteral formula used, the types of scoring systems used to define disease activity and remission, the duration of interventions, the length of follow-up, and the use of concomitant medications. Also, the included trials were on total enteral nutrition (not partial enteral nutrition)
d. Small sample size (n = 435) and low event rates (n = 162 for relapse). Optimal information size not met.
e. Downgraded for risk of bias due to unclear randomization sequence, lack of blinding, and incomplete outcome data with high withdrawal rates (36%).
f. Downgraded for indirectness. This study compared partial enteral nutrition against total enteral nutrition with no placebo / other treatment arms.
g. Small sample size (n = 50) and low event rates (n = 14). Optimal information size not met.

h. Unexplained statistical heterogeneity (I^2 = 46%)
i. Small sample size (n = 233) and low event rates (n = 58). Optimal information size not met.
j. Overall quality of evidence is anchored on efficacy and safety data in adult population with support of pediatric data.

statement #11

Evidence for statement #11: In patients with Crohn's disease in remission, we suggest that if partial enteral nutrition is used it should be combined with other medications to maintain clinical remission.

PICO: In patients with Crohn's disease in remission, should partial enteral nutrition (PEN) alone vs. PEN combined with other medications be used to maintain clinical remission?

PICO: In patients with Crohn's disease in remission, should partial enteral nutrition (PEN) alone vs. other medications be used to maintain clinical remission?

Quality assessment								Summary of findings				Comments
Studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Quality of evidence	Overall quality of evidence	No of patients (ITT)		Effect		
								PEN	Regular diet +/- other medications	Relative (95% CI)	Absolute (95% CI)	
Clinical Remission (Maintenance): relative to regular diet +/- other medications (follow up: 6 months to 2 years) (**CRITICAL** for decision making)							⊕⊖⊖⊖ **VERY LOW** [e]					
1 SR (3 RCTs)[31] *Adult population*	Serious [a]	Not serious	Very serious [b]	Serious [c]	None	⊕⊖⊖⊖ **VERY LOW**		Meta-analysis was not possible due to substantial differences in study designs				No significant difference in clinical remission between PEN vs. the comparator groups (regular diet +/- other medications).
Adverse events: relative to regular diet +/- other medications (follow up: 5 months to 2 years) **(IMPORTANT)** for decision making)												
1 SR (1 RCT)[31] *Adult population*	Serious [a]	Not serious	Very serious [b]	Very Serious [d]	None	⊕⊖⊖⊖ **VERY LOW**		Meta-analysis was not possible due to substantial differences in study designs				The majority of adverse events reported with PEN were mild and mainly gastrointestinal. Intolerance, and lack of compliance were also reported.

a. Most trials had unclear risk of bias for allocation concealment and randomization, lack of blinding, and incomplete outcome data with high withdrawal rates, particularly in the PEN arms.
b. Downgraded for indirectness. There was wide variation in disease activity, onset of disease and disease location in recruited subjects. There were also variations in study design, the patient populations (as to how induction was achieved), the types and quantity of enteral formula used, comparators used, the duration of interventions, the length of follow-up, and the use of concomitant medications. Also, 2/3 studies were Japanese. Generalizability of findings to other populations may be limited.
c. Small sample size (n = 196) and low event rates (n = 105 for relapse). Optimal information size not met.
d. Small sample size (n = 62) and low event rates (n = 8). Optimal information size not met.
e. Overall quality of evidence is anchored on efficacy and safety data in adult population with no available pediatric data.

IMMUNOSUPPRESSANTS

Statement #12

Evidence for statement #12: In patients with Crohn's disease of any severity, we recommend against thiopurine monotherapy to induce clinical remission.

PICO: In patients with Crohn's disease of any severity, should thiopurine monotherapy vs. placebo be used to induce clinical remission?

Quality assessment								Summary of findings				Comments
								No of patients (ITT)		Effect		
Studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Quality of evidence	Overall quality of evidence	Thiopurine	Placebo	Relative (95% CI)	Absolute (95% CI)	
Failure to Achieve Clinical Remission (Induction): relative to placebo (follow up: 12 - 17 weeks) (**CRITICAL** for decision making)							⊕⊖⊖⊖ **VERY LOW** [e]					
2 SRs (5 RCTs)[32, 33] *Adult population*	Serious [a]	Not serious [b]	Serious [c]	Serious [d]	None	⊕⊖⊖⊖ **VERY LOW**		102/197 (51.8%)	115/183 (62.8%) Placebo	RR 0.87 (0.71 to 1.06)	82 fewer per 1,000 (from 38 more to 182 fewer)	No statistically significant difference in failure to clinical remission between thiopurines and placebo.
Adverse events: relative to placebo (follow up: 12-17 weeks) **(IMPORTANT)** for decision making)												
2 SRs (2 RCT)[32, 33] *Adult population*	Serious [a]	Not serious	Serious [c]	Serious [d]	None	⊕⊖⊖⊖ **VERY LOW**		15/111 (13.5%)	4/105 (3.8%) Placebo	RR 2.56 (0.92 to 7.13)	60 more per 1,000 (from 3 fewer to 234 more)	No statistically significant difference in adverse events between thiopurines and placebo.

a. Most trials had unclear risk of bias for sequence generation and/or allocation concealment.
b. No statistical heterogeneity ($I^2 = 21\%$)
c. Downgraded for indirectness. Four of the five trials also gave a tapering dose of steroid therapy so the assessment of efficacy of thiopurine is in the context of additional benefit to steroids alone (not thiopurine monotherapy). No pediatric data.
d. Downgraded for imprecision as the 95% CI crosses the clinical decision threshold between recommending and not recommending thiopurine (i.e. clinical action would differ if the upper versus the lower boundary of the CI represented the truth).
e. Overall quality of evidence is anchored on efficacy and safety data in adult population with no available pediatric data.

Statement #13

Evidence for statement #13: In female patients with Crohn's disease, we suggest a thiopurine to maintain remission.

PICO: In female patients with Crohn's disease, should thiopurine vs. placebo be used to maintain clinical remission?

No Recommendation F

Evidence for No Recommendation F. In male patients with Crohn's disease, the consensus group does not make a recommendation (for or against) regarding use of thiopurine to maintain remission.

PICO: In male patients with Crohn's disease, should thiopurine vs. placebo be used to maintain clinical remission?

Quality assessment								Summary of findings				
								No of patients (ITT)		Effect		
Studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Quality of evidence	Overall quality of evidence	Thiopurine	Placebo	Relative (95% CI)	Absolute (95% CI)	Comments
Clinical Remission (Maintenance): relative to placebo (follow up: 6 – 18 months) (**CRITICAL** for decision making)							⊕⊖⊖⊖ **VERY LOW**					
2 SRs (6 RCTs)[32, 38] *Adult population*	Serious [a]	Not serious [b]	Serious [c]	Serious [d]	None			161/220 (73.2%)	166/269 (61.7%)	**RR 1.19 (1.05 to 1.34)**	**117 more per 1,000 (from 31 more to 210 more)**	Azathioprine is superior to placebo for maintenance of clinical remission.
Clinical relapse (Maintenance): relative to placebo (follow up: 2 years) (**CRITICAL** for decision making)												
1 RCT[39] *Adult population*	Serious [e]	Not serious	Serious [f]	Serious [g]	None		⊕⊖⊖⊖ **VERY LOW**	4/26 (15.4%)	8/26 (30.8%)	RR 0.50 (0.17 to 1.46)	154 fewer per 1,000 (from 142 more to 255 fewer)	No significant difference in relapse between AZA vs. placebo after 2 years.
Clinical relapse (Maintenance): relative to placebo (follow up: 18 months) (**CRITICAL** for decision making)												
1 RCT[40] *Pediatric population*	Not serious	Not serious	Serious [h]	Serious [i]	None		⊕⊕⊖⊖ **LOW**	3/27 (11.1%)	13/28 (46.4%)	**RR 0.24 (0.08 to 0.75)**	**353 fewer per 1,000 (from 116 fewer to 427 fewer)**	Azathioprine is superior to placebo for in reducing relapse.
Clinical remission (Maintenance) (follow up 6 and 12 months) (**CRITICAL** for decision making)												
1 Observational study[41] *Pediatric population*	Very serious [j]	Not serious	Very serious [k]	Serious [l]	None		⊕⊖⊖⊖ **VERY LOW**	15/65 (23%) remained in clinical remission at 12 months				
Adverse events: relative to placebo (follow up: 12- 18 months) **(IMPORTANT)** for decision making)												
2 SRs (6 RCTs)[32, 38] *Adult population*	Serious [a]	Not serious [b]	Serious [c]	Serious [m]	None		⊕⊖⊖⊖ **VERY LOW**	61/186 (32.8%)	43/173 (24.9%)	**RR 1.29 (1.02 to 1.64)**	**72 more per 1,000 (from 5 more to 159 more)**	Significantly more adverse events with Azathioprine than with placebo.

							⊕⊖⊖⊖ **VERY LOW** [n]					

a. Most trials had unclear risk of bias for sequence generation and/or allocation concealment.
b. No statistical heterogeneity ($I^2 = 0\%$)
c. Downgraded for indirectness. Most of the trials included patients who achieved clinical remission on thiopurines and steroids (during the induction phase of the same study) or patients who were already in remission while on thiopurines (withdrawal studies). Such patients are more likely to respond to thiopurines and less likely to experience adverse events.
d. Small sample size (n = 489) and low event rates (n = 162 for relapse). Optimal information size not met.
e. Unclear risk of bias for allocation concealment.
f. Downgraded for indirectness. This trial included patients who had achieved clinical remission on thiopurines (withdrawal study).
g. Small sample size (n = 52) and low event rates (n = 12). Optimal information size not met. Downgraded for imprecision as the 95% CI crosses the clinical decision threshold between recommending and not recommending thiopurine (i.e. clinical action would differ if the upper versus the lower boundary of the CI represented the truth).
h. Downgraded for indirectness. This trial used 6-mercaptopurine and steroid tapering as induction (not with steroids alone or EEN).
i. Small sample size (n = 55) and low event rates (n = 16). Optimal information size not met.
j. Downgraded for risk of bias. High risk for selection bias. Patients with more severe disease may be preferentially started on thiopurines. Medication adherence was not captured. There was 25% loss to follow-up.

k. Downgraded for indirectness. Large variations in practice pattern among practitioners including thiopurine dosage, decisions about continuing thiopurines, need for additional medications, frequency of follow-up, and outcome assessment (physician global assessment as mild, moderate, severe).
l. Small sample size (n = 65) and low event rates (n = 15).
m. Small sample size (n = 359) and low event rates (n = 104).
n. Overall quality of evidence is anchored on efficacy and safety data in adult population with support of pediatric data.

Statement #14

Evidence for statement #14: In patients with Crohn's disease, we suggest that testing for TPMT be done prior to initiating thiopurine therapy to guide dosing.

PICO: In patients with Crohn's disease, should TPMT testing vs. no TPMT testing be done prior to initiating thiopurine therapy to guide dosing (to increase the rates of clinical remission and reduce the rates of adverse events)?

Quality assessment								Summary of findings				Comments
								No of patients (ITT)		Effect		
Studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Quality of evidence	Overall quality of evidence	TPMT testing	No TPMT testing	Relative (95% CI)	Absolute (95% CI)	
Clinical remission: relative to no TPMT testing (follow up: 20 weeks) (**CRITICAL** for decision making)							⊕⊖⊖⊖ **VERY LOW**[f]					
1 RCT[42] *Adult population*	Serious [a]	Not serious	Serious [b]	Serious [c]	None	⊕⊖⊖⊖ **VERY LOW**		55/405 (13.6%)	58/378 (15.3%)	RR 1.03 (0.84 to 1.27)	5 more per 1,000 (from 25 fewer to 41 more)	No statistically significant difference in clinical remission between TPMT testing and no testing.
Hematologic events: relative to no TPMT testing (follow up: up to 24 weeks) **(IMPORTANT)** for decision making)												
1 SR (3 RCTs)[42-44] *Adult population*	Serious [a]	Not serious [d]	Serious [e]	Serious [c]	None	⊕⊖⊖⊖ **VERY LOW**		32/586 (5.5%)	32/559 (5.7%)	RR 0.94 (0.59 to 1.51)	3 fewer per 1,000 (from 23 fewer to 29 more)	No statistically significant difference in hematologic events between TPMT testing and no testing.

a. All trials were not blinded. Treatment decisions and monitoring of adverse events were left to the discretion of the treating physicians. High risk for performance bias. Very high withdrawal rates.
b. Downgraded for indirectness. No pediatric data.
c. Downgraded for imprecision as the 95% CI crosses the clinical decision threshold between recommending and not recommending TPMT testing (i.e. clinical action would differ if the upper versus the lower boundary of the CI represented the truth).
d. No statistical heterogeneity ($I^2 = 0\%$)
e. Downgraded for indirectness. Surrogate outcomes – hematologic adverse events and treatment discontinuation were used (not patient important outcomes such as death, serious infections, etc). No pediatric data.
f. Overall quality of evidence is anchored on efficacy and safety data in adult population with no available pediatric data.

No consensus G

Evidence for No consensus G: In patients with mild to moderate Crohn's disease, the consensus group does not make a recommendation (for or against) regarding methotrexate monotherapy to induce clinical remission.

PICO: In patients with mild to moderate Crohn's disease, should methotrexate monotherapy vs. placebo be used to induce clinical remission?

Quality assessment								Summary of findings				Comments
Studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Quality of evidence	Overall quality of evidence	No of patients (ITT) Methotrexate	No of patients (ITT) Placebo	Effect Relative (95% CI)	Effect Absolute (95% CI)	
Failure to Achieve Clinical Remission (Induction): relative to placebo (follow up: 17 weeks) (**CRITICAL** for decision making)							⊕⊖⊖⊖ **VERY LOW**					
1 SR (2 RCTs)[32] *Adult population*	Serious [a]	Not serious [b]	Serious [c]	Serious [d]	None			76/120 (63.3%)	58/73 (79.5%) Placebo	RR 0.82 (0.65 to 1.03)	143 fewer per 1,000 (from 24 more to 278 fewer)	No statistically significant difference in failure to achieve clinical remission between Methotrexate and placebo.
Clinical Remission (follow up: < 3 months) (**CRITICAL** for decision making)							⊕⊖⊖⊖ **VERY LOW** [i]					
1 SR (10 case series)[34] *Pediatric population*	Very serious [e]	Not serious	Very serious [f]	Serious [g]	None			Oral or subcutaneous Methotrexate q weekly had remission rates of 57% at 1 month and 29% and 70% at 3 months.				
Withdrawal due to adverse events: relative to placebo (follow up: 17 weeks) **(IMPORTANT)** for decision making)												
1 SR (3 RCTs)[35] *Adult population*	Serious [a]	Not serious	Serious [c]	Serious [h]	None			20/135 (14.8%)	1/91 (1.1%) Placebo	Meta-analysis was not possible		Significantly more adverse events with Methotrexate than with placebo

a. Most trials had unclear risk of bias for sequence generation and allocation concealment.
b. No statistical heterogeneity ($I^2 = 33\%$)
c. Downgraded for indirectness. Serious variability with respect to participants (severity not reported), interventions, dose and treatment duration, concomitant medications, and outcomes to the extent that meta-analysis was considered to be inappropriate in the Cochrane review.[35] No pediatric data.
d. Downgraded for imprecision as the 95% CI crosses the clinical decision threshold between recommending and not recommending methotrexate (i.e. clinical action would differ if the upper versus the lower boundary of the CI represented the truth).
e. Downgraded for risk of bias. Retrospective chart review (case series) with no control arms. High risk for selection bias, ascertainment bias, performance and detection bias. Clinical scoring systems for disease activity were generally calculated retrospectively, and therefore, may not accurately reflect patient status.
f. Downgraded for indirectness. Varying patient populations, location and severity of disease, interventions, concomitant therapies, methotrexate dosing regimens, duration of follow-up, and definitions of remission. Most patients had prior thiopurine exposure.
g. Small sample size (n = 771) and low event rates (n = 224).
h. Small sample size (n = 226) and low event rates (n = 21).
i. Overall quality of evidence is anchored on efficacy and safety data in adult population with support of pediatric data.

No consensus H

Evidence for No consensus H: In patients with Crohn's disease, the consensus group does not make a recommendation (for or against) regarding oral methotrexate to maintain clinical remission.

PICO: In patients with Crohn's disease, should oral methotrexate vs. placebo be used to maintain clinical remission?

Statement #15

Evidence for statement #15: In patients with Crohn's disease, we suggest parenteral methotrexate to maintain clinical remission.

PICO: In patients with Crohn's disease, should parenteral methotrexate vs. placebo be used to maintain clinical remission?

Quality assessment								Summary of findings				Comments
								No of patients (ITT)		Effect		
Studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Quality of evidence	Overall quality of evidence	Methotrexate	Placebo	Relative (95% CI)	Absolute (95% CI)	
Clinical Remission (Maintenance): relative to placebo (follow up: 40 weeks) (**CRITICAL** for decision making)												
2 SR (2 RCTs)[32, 36] *Adult population*	Serious [a]	Not serious [b]	Serious [c]	Serious [d]	None	⊕⊖⊖⊖ **VERY LOW**	⊕⊖⊖⊖ **VERY LOW** [l]	26/40 (65.0%) IM	14/36 (38.9%)	**RR 1.67 (1.05 to 2.67)**	**261 more per 1,000 (from 19 more to 649 more)**	Methotrexate IM is superior to placebo for maintenance of clinical remission.
						⊕⊖⊖⊖ **VERY LOW**		9/10 (90.0%) Oral	8/12 (66.7%)	RR 1.35 (0.86 to 2.12)	233 more per 1,000 (from 93 fewer to 747 more)	No significant difference between oral Methotrexate and placebo for maintenance of clinical remission.
Clinical Remission (**Maintenance)** (follow up: 1 year) (**CRITICAL** for decision making)												
1 SR (10 case series)[34] *Pediatric population*	Very serious [e]	Not serious	Very serious [f]	Serious [g]	None	⊕⊖⊖⊖ **VERY LOW**		Oral or subcutaneous Methotrexate q weekly had remission rates of 25-53% at 1 year.				
Serious adverse events: relative to placebo (follow up: 40 weeks) **(IMPORTANT)** for decision making)												
2 SR (2 RCTs)[32, 36] *Adult population*	Serious [a]	Not serious [b]	Serious [c]	Serious [h]	None	⊕⊖⊖⊖ **VERY LOW**		1/50 (2.0%) Oral / IM	2/48 (4.2%) Placebo	Meta-analysis was not performed due to heterogeneity in clinical designs.		No significant difference in serious adverse events between Methotrexate and placebo.
1 SR (20 case series)[37] *Pediatric population*	Very serious [e]	Not serious	Very serious [j]	Serious [k]	None	⊕⊖⊖⊖ **VERY LOW**		Pooled proportion of patients with abnormal liver biochemistry was 10.2% (5.4-18.5%)				

a. Both trials had unclear risk of bias for random sequence generation and allocation concealment.

b. No serious inconsistency if oral versus parental Methotrexate are considered separately.
c. Downgraded for indirectness. All trials included patients who had previously chronic steroid dependent active Crohn's disease, and were not induced into clinical remission with either steroids / EEN. They were induced into remission with Methotrexate and steroid tapering. No pediatric data.
d. Small sample size and low event rates. Optimal information size not met.
e. Downgraded for risk of bias. Retrospective chart review (case series) with no control arms. High risk for selection bias, ascertainment bias, performance and detection bias. Clinical scoring systems for disease activity were generally calculated retrospectively, and therefore, may not accurately reflect patient status.
f. Downgraded for indirectness. Serious variability with respect to participants (severity not reported), interventions, dose and treatment duration, concomitant medications, and outcomes to the extent that meta-analysis was considered to be inappropriate in the Cochrane review.[35] No pediatric data.
g. Small sample size (n = 771) and low event rates (n = 224).
h. Small sample size (n = 98) and low event rates (n = 3).
i. Downgraded for risk of bias. Retrospective chart review (case series) with no control arms. High risk for selection bias, ascertainment bias, performance and detection bias.
j. Downgraded for indirectness. Serious variability with respect to participants (severity not reported), interventions, dose and treatment duration, concomitant medications.
k. Small sample size (n = 457) and low event rates.
l. Overall quality of evidence is anchored on efficacy and safety data in adult population with support of pediatric data.

Statement #16

Evidence for statement #16: In patients with Crohn's disease who are in clinical remission with a thiopurine or methotrexate as maintenance therapy, we suggest assessment for mucosal healing within the first year to determine the need to modify therapy if significant ulcerations persist.

PICO: In patients with Crohn's disease who are in clinical remission with a thiopurine or methotrexate as maintenance therapy, should assessment for mucosal healing within the first year vs. no assessment for mucosal healing be done (to increase the rates of clinical remission and reduce the rates of adverse events)?

No consensus I

Evidence for No consensus I. In patients with moderate to severe inflammatory Crohn's disease who have achieved clinical remission but not mucosal healing with a corticosteroid, thiopurine, or methotrexate, the consensus group does not make a recommendation (for or against) regarding anti-TNF therapy to induce and maintain mucosal healing.

PICO: In patients with moderate to severe inflammatory Crohn's disease who have achieved clinical remission but not mucosal healing with a corticosteroid, thiopurine, or methotrexate, should anti-TNF therapy vs. no anti-TNF therapy be used to induce and maintain mucosal healing (to increase the rates of clinical remission and reduce the rates of adverse events)?

Quality assessment								Summary of findings				Comments
Studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Quality of evidence	Overall quality of evidence	No of patients (ITT)		Effect		
								Mucosal healing	No mucosal healing	Relative (95% CI)	Absolute (95% CI)	
Clinical Remission: relative to placebo (follow up: at least 50 weeks) (**CRITICAL** for decision making)												
1 SR (10 cohort studies)[45] *Adult and Pediatric population*	Very serious [a]	Not serious [b]	Very serious [c]	Serious [c]	None	⊕⊖⊖⊖ **VERY LOW**	⊕⊖⊖⊖ **VERY LOW** [e]	193/280 (68.9%)	131/308 (42.5%)	**OR 2.80 (1.91-4.10)**	**249 more per 1,000 (from 160 more to 327 more)**	Mucosal healing is associated with long-term clinical remission. Sensitivity analysis showed no difference in outcomes if mucosal healing was achieved on biologics vs. non-biologics.

a. Downgraded for risk of bias. Limited by potential residual confounding factors and selection bias.
b. No statistical heterogeneity ($I^2 = 0\%$)
c. Downgraded for indirectness. Mucosal healing is a surrogate outcome for patient important outcomes such as clinical remission, reduced risk of hospitalization or surgery. Observational data suggested that achieving mucosal healing is associated with improved clinical outcomes. Mucosal healing is therefore an important prognostic sign regarding disease course and response to treatment. However, no studies have compared the benefits and risks of achieving mucosal healing versus clinical remission alone or endoscopic remission alone. Also, serious variability with respect to participants (severity, phenotypes, duration of disease), concomitant medications, interventions used to assess mucosal healing, and timing of endoscopy or imaging studies. Included 3 pediatric studies.
d. Small sample size (n = 588).
e. Overall quality of evidence is anchored on data in adult population with support of pediatric data.

ANTI-TNFs

Statement #17

Evidence for statement #17: In patients with moderate to severe inflammatory Crohn's disease who have failed to achieve clinical remission with corticosteroids, we recommend anti-TNF therapy (adalimumab, infliximab) to induce and maintain clinical remission.

PICO: In patients with moderate to severe inflammatory Crohn's disease who have failed to achieve clinical remission with corticosteroids, should anti-TNF therapy vs. placebo be used to induce and maintain clinical remission?

Statement #18

Evidence for statement #18: In patients with moderate to severe inflammatory Crohn's disease who fail to achieve or maintain clinical remission with a thiopurine or methotrexate, we recommend anti-TNF therapy (adalimumab, infliximab) to induce and maintain clinical remission.

PICO: In patients with moderate to severe inflammatory Crohn's disease who fail to achieve or maintain clinical remission with a thiopurine or methotrexate, should anti-TNF therapy vs. placebo be used to induce and maintain clinical remission?

Quality assessment								Summary of findings				Comments
								No of patients (ITT)		Effect		
Studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Quality of evidence	Overall quality of evidence	Anti-TNF	Placebo	Relative (95% CI)	Absolute (95% CI)	
Failure to Achieve Clinical Remission (Induction): relative to placebo (follow up: 4-12 weeks) (**CRITICAL** for decision making)							⊕⊕⊕⊕ **HIGH** [f]					
3 SR (10 RCTs)[46-48] *Adult Population*	Not serious	Not serious [a]	Serious [b]	Not serious	None	⊕⊕⊕⊖ **MODERATE**		1142/1598 (71.5%)	935/1158 (80.7%)	**RR 0.87 (0.80 to 0.94)**	**105 fewer per 1,000 (from 48 fewer to 161 fewer)**	Anti-TNF was superior to placebo for inducing clinical remission in active Crohn's disease.
Relapse (Maintenance): **relative to placebo** (follow up: 26-60 weeks) (**CRITICAL** for decision making)												
2 SR (5 RCTs)[46, 47] *Adult and pediatric population*	Not serious	Not serious [c]	Not serious [d]	Not serious	None	⊕⊕⊕⊕ **HIGH**		472/844 (55.9%)	428/546 (78.4%)	**RR 0.71 (0.65 to 0.76)**	**227 fewer per 1,000 (from 188 fewer to 274 fewer)**	Anti-TNF was superior to placebo for maintenance of clinical remission in Crohn's disease.
Adverse events (Induction): relative to placebo (follow up: 4-12 weeks) **(IMPORTANT** for decision making)												
3 SR (7 RCTs)[46-48] *Adult Population*	Not serious	Not serious	Serious [b]	Not serious	None	⊕⊕⊕⊖ **MODERATE**		863/1279 (67.5%)	630/940 (67.0%)	RR 0.99 (0.90 to 1.08)	7 fewer per 1,000 (from 54 more to 67 fewer)	No statistically significant difference in adverse events between anti-TNF and placebo.
Adverse events (Maintenance): relative to placebo (follow up 26-60 weeks) (**IMPORTANT** for decision making)												
2 SR (3 RCTs)[46, 47] *Adult Population*	Not serious	Not serious	Serious [e]	Not serious	None	⊕⊕⊕⊖ **MODERATE**		204/290 (70.3%)	196/266 (73.7%)	RR 0.93 (0.84 to 1.03)	54 fewer per 1,000 (from 22 more to 118 fewer)	No statistically significant difference in adverse events between anti-TNF and placebo.

a. Not downgraded for inconsistency. Statistical heterogeneity (I^2 = 78%) for Infliximab, but no statistical heterogeneity for Adalimumab or Certolizumab.
b. Downgraded for indirectness. No RCTs for children in Crohn's disease to induce remission.
c. Not downgraded for inconsistency. Statistical heterogeneity (I^2 = 70%) for Adaliumamb, but no statistical heterogeneity for Infliximab.
d. Not downgraded for indirectness. 1 RCT evaluating 112 children assessed Infliximab for maintenance (in responders) with similar effect seen as in adults.
e. Downgraded for indirectness. No RCTs for children.
f. Overall quality of evidence is anchored on efficacy and safety data in adult population with support of pediatric data.

Statement #19

Evidence for statement #19: In patients with severe inflammatory Crohn's disease judged at risk for progressive, disabling disease, we suggest anti-TNF therapy as first-line therapy to induce and maintain clinical remission.

PICO: In patients with severe inflammatory Crohn's disease judged at risk for progressive, disabling disease, should anti-TNF therapy as first-line therapy vs. placebo or other treatments be used to induce and maintain clinical remission?

Also see evidence for statements #17 and #18.

Quality assessment								Summary of findings				Comments
								No of patients (ITT)		Effect		
Studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Quality of evidence	Overall quality of evidence	Early Combination Anti-TNF + Immunomodulator	Conventional management	Relative (95% CI)	Absolute (95% CI)	
Clinical Remission (Induction): relative to placebo (follow up: 26 weeks) (**CRITICAL** for decision making)							⊕⊖⊖⊖ **VERY LOW** [f]					
1 RCT[49] *Adult population*	Serious [a]	Not serious	Serious [b]	Serious [c]	None	⊕⊖⊖⊖ **VERY LOW**		39/65 (60.0%) Early combined Anti-TNF + Azathioprine	23/64 (35.9%) Conventional management with steroids, followed by Azathioprine and Anti-TNF	**RR 1.67 (1.14 to 2.45)**	**241 more per 1,000 (from 50 more to 521 more)**	Early combined immunosuppressive was more effective than conventional management for induction of clinical remission.
Clinical Remission (Maintenance): **relative to placebo** (follow up: 52 weeks) (**CRITICAL** for decision making)												
1 RCT[49] *Adult population*	Serious [a]	Not serious	Serious [b]	Serious [d]	None	⊕⊖⊖⊖ **VERY LOW**		40/65 (61.5%) Early combined Anti-TNF + Azathioprine	27/64 (42.2%) Conventional management with steroids, followed by Azathioprine and Anti-TNF	**RR 1.46 (1.03 to 2.06)**	**194 more per 1,000 (from 13 more to 447 more)**	Early combined immunosuppression was more effective than conventional management for maintenance of clinical remission.
Clinical Remission (Maintenance): (follow up: 1 year) (**IMPORTANT** for decision making)												
1 Observational Cohort Study[50] *Pediatric population*	Serious [e]	Not serious	Serious [f]	Not serious	None	⊕⊖⊖⊖ **VERY LOW**		**E**arly treatment with anti-TNFs was superior to early treatment with an immunomodulator (85.3% vs. 60.3% in remission; RR 1.41 (1.14 to 1.75)				
Adverse events (Induction and Maintenance): relative to placebo (follow up 52 weeks) (**IMPORTANT** for decision making)												
1 RCT[49] *Adult population*	Serious [a]	Not serious	Serious [b]	Serious [e]	None	⊕⊖⊖⊖ **VERY LOW**		20/65 (30.8%) Early combined Anti-TNF + Azathioprine	19/64 (29.7%) Conventional management with steroids, followed by Azathioprine and Anti-TNF	RR 1.04 (0.61 to 1.75)	12 more per 1,000 (from 116 fewer to 223 more)	No statistically significant difference in adverse events between early combined immunosuppression and conventional

												management for induction and maintenance of clinical remission.

a. Open unblinded trial. High risk for performance and detection bias.
b. Downgraded for indirectness. No pediatric data.
c. Small sample size (n = 129) and low event rates (n = 62).
d. Small sample size (n = 129) and low event rates (n = 67)
e. Downgraded for risk of bias. Limited by potential residual confounding factors, selection bias and detection bias.
f. Downgraded for indirectness. Variations in disease phenotype, location and severity, concomitant medications, dosing of anti-TNF agents and immunosuppressives, interventions, and definition of clinical remission.
g. Small sample size (n = 129) and low event rates (n = 39)
h. Overall quality of evidence is anchored on efficacy and safety data in adult population with support of pediatric data.

Statement #20

Evidence for statement #20: When starting infliximab in <u>males</u>, we suggest <u>against</u> using it in combination with a thiopurine.

PICO: In males with Crohn's disease, should infliximab or combination therapy with a thiopurine be used to induce and maintain clinical remission?

No Recommendation J

Evidence for No Recommendation J. When starting infliximab in females, the consensus group does not make a recommendation (for or against) regarding combining it with a thiopurine to maintain a durable clinical remission.

PICO: In females with Crohn's disease, should infliximab or combination therapy with a thiopurine be used to induce and maintain clinical remission?

Quality assessment								Summary of findings				Comments
								No of patients (ITT)		Effect		
Studies	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Quality of evidence**	**Overall quality of evidence**	**Combination therapy with Infliximab and Thiopurine**	**Infliximab alone**	**Relative (95% CI)**	**Absolute (95% CI)**	
Clinical Remission (Induction) (follow up: 26 weeks) (**CRITICAL** for decision making)												
1 RCT[51] 2 SR (1 RCT)[52, 53] *Adult population*	Not serious	Not serious	Serious [a]	Serious [b]	None	⊕⊕⊖⊖ **LOW**	⊕⊕⊖⊖ **LOW**	96/169 (56.8%) Infliximab + Azathioprine	75/169 (44.4%) Infliximab alone	**RR 1.28 (1.03 to 1.59)**	**124 more per 1,000 (from 13 more to 262 more)**	Combination therapy with Infliximab and Azathioprine was superior to Infliximab alone for induction of clinical remission.
Loss of Clinical Response (Maintenance) (follow up: 54 weeks) (**CRITICAL** for decision making)												

1 RCT[54] *Pediatric population*	Serious [c]	Not serious	Not serious	Very Serious [d]	None	⊕⊖⊖⊖ **VERY LOW**		3/45 (4.4%) Infliximab + Azathioprine or Methotrexate	2/39 (5.1%) Infliximab alone	RR 0.87 (0.13 to 5.87)	7 fewer per 1,000 (from 45 fewer to 250 more)	No statistically significant difference in loss of clinical response between Infliximab and Azathioprine or Methotrexate vs. Infliximab alone.
Clinical Remission (Maintenance): (follow up: 6 months) (**IMPORTANT** for decision making)												
1 SR[55] (observational data from 2 RCTs) *Adult population*	Not serious	Not serious [e]	Serious [a]	Serious [f]	None	⊕⊖⊖⊖ **VERY LOW**		40/71 (56.3%) Infliximab + Azathioprine or Methotrexate	68/165 (41.2%) Infliximab alone	OR 1.73 (0.97 to 3.07)	136 more per 1,000 (from 7 fewer to 271 more)	No statistically significant difference in clinical remission between Infliximab and immunomodulator vs. Infliximab alone.
Adverse events (Induction): (follow up 26 weeks) (**IMPORTANT** for decision making)												
1 RCT[51] *Adult population*	Not serious	Not serious	Serious [a]	Serious [g]	None	⊕⊕⊖⊖ **LOW**		37/169 (23.1%) Infliximab + Azathioprine	29/169 (16.0%) Infliximab alone	RR 1.44 (0.93 to 2.25)	70 more per 1,000 (from 11 fewer to 200 more)	No statistically significant difference in adverse events between Infliximab and Azathioprine vs. Infliximab alone.

a. Downgraded for indirectness. No pediatric data.
b. Small sample size (n = 169) and low event rates (n = 96).
c. This trial was open-label and unblinded. High risk for performance and detection bias.
d. Downgraded for imprecision as the 95% CI crosses the clinical decision threshold between recommending and not recommending combination therapy (i.e. clinical action would differ if the upper versus the lower boundary of the CI represented the truth).
e. No statistical heterogeneity (I^2 = 0%) for Infliximab.
f. Small sample size (n = 236) and low event rates (n = 108).
g. Small sample size (n = 169) and low event rates (n = 66)
h. Overall quality of evidence is anchored on efficacy and safety data in adult population. Although pediatric data is available, the results differ from the adult data RCT data. This could be due to the fact that both arms in the pediatric RCT were receiving combination therapy for the first 10 weeks, and duration of the study may be too short to see any meaningful differences between groups. If we take into account this inconsistency between adult RCT vs. pediatric RCT or adult observational data, we would downgrade for inconsistency (but not indirectness). Either way, the overall quality of evidence remains low.

Statement #21

Evidence for statement #21: When starting adalimumab in <u>males</u>, we suggest <u>against</u> using it in combination with a thiopurine.

PICO: In males with Crohn's disease, should adalimumab alone or combination therapy with a thiopurine be used to induce and maintain clinical remission?

No Recommendation K

Evidence for No Recommendation K: When starting adalimumab in <u>females</u>, the consensus group does not make a recommendation (for or against) regarding combining it with a thiopurine to maintain a durable clinical remission.

PICO: In females with Crohn's disease, should adalimumab alone or combination therapy with a thiopurine be used to induce and maintain clinical remission?

Quality assessment								Summary of findings				Comments
								No of patients (ITT)		Effect		
Studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Quality of evidence	Overall quality of evidence	Combination therapy with Adalimumab and Thiopurine	Adalimumab alone	Relative (95% CI)	Absolute (95% CI)	
Clinical Remission (Induction) (follow up: 26 weeks) (**CRITICAL** for decision making)							⊕⊖⊖⊖ **VERY LOW**					
1 RCT[56] *Adult population*	Serious [a]	Not serious	Serious [b]	Very serious [c]	None	⊕⊖⊖⊖ **VERY LOW**		62/91 (68.1%) Adalimumab + Azathioprine	61/85 (71.8%) Adalimumab alone	RR 0.95 (0.78 to 1.15)	36 fewer per 1,000 (from 108 more to 158 fewer)	No statistically significant difference in clinical remission between Adalimumab and Azathioprine vs. Adalimumab alone.
Clinical Remission (Maintenance) (follow up: 52 weeks) (**CRITICAL** for decision making)												
1 RCT[56] *Adult population*	Serious [a]	Not serious	Serious [b]	Very serious [d]	None	⊕⊖⊖⊖ **VERY LOW**		62/91 (68.1%) Adalimumab + Azathioprine	64/85 (75.3%) Adalimumab alone	RR 0.90 (0.75 to 1.09)	75 fewer per 1,000 (from 68 more to 188 fewer)	No statistically significant difference in clinical remission between Adalimumab and Azathioprine vs. Adalimumab alone.
Clinical Remission (Induction): (follow up: 26 weeks) (**IMPORTANT** for decision making)							⊕⊖⊖⊖ **VERY LOW**					
1 Observational Cohort study[57] *Pediatric population*	Serious [e]	Not serious	Not serious	Very serious [f]	None	⊕⊖⊖⊖ **VERY LOW**		No statistically significant difference in clinical remission between Adalimumab and Immunomodulator (Azathioprine / Methotrexate) vs. Adalimumab alone (35.9% vs. 29.6%).				No statistically significant difference in clinical remission between Adalimumab and immunomodulator vs. Adalimumab alone.
Adverse events (Maintenance): (follow up 52 weeks) (**IMPORTANT** for decision making)												
1 RCT[56] *Adult population*	Serious [a]	Not serious	Serious [b]	Very serious [g]	None	⊕⊖⊖⊖ **VERY LOW**		22/91 (24.2%) Adalimumab + Azathioprine	19/85 (22.4%) Adalimumab alone	RR 1.08 (0.63 to 1.85)	18 more per 1,000 (from 83 fewer to 190 more)	No statistically significant difference in adverse events between Adalimumab and Azathioprine vs. Adalimumab alone.

a. This trial was open-label and un-blinded. High risk for performance and detection bias. High withdrawal rates due to adverse events in both arms (26% in monotherapy and 32% in combination).
b. Downgraded for indirectness. No pediatric data.
c. Downgraded for imprecision as the 95% CI crosses the clinical decision threshold between recommending and not recommending combination therapy (i.e. clinical action would differ if the upper versus the lower boundary of the CI represented the truth).
d. Small sample size (n = 176) and low event rates (n = 50 not in clinical remission).
e. Subgroup analysis of the IMAgINE trial. Unclear whether prognostic factors are balanced.
f. Small sample size (n = 188) and low event rates (n = 63 clinical remission).
g. Downgraded for imprecision as the 95% CI crosses the clinical decision threshold between recommending and not recommending combination therapy (i.e. clinical action would differ if the upper versus the lower boundary of the CI represented the truth).

h. Overall quality of evidence is anchored on efficacy and safety data in adult population with support of pediatric data.

Statement #22

Evidence for statement #22: In <u>male</u> patients with Crohn's disease receiving immunomodulatory therapy in combination with an anti-TNF therapy, we suggest methotrexate in preference to thiopurines.

PICO: In males with Crohn's disease, should anti-TNF therapy alone or combination therapy with a methotrexate be used to induce and maintain clinical remission?

Quality assessment								Summary of findings				Comments
								No of patients (ITT)		Effect		
Studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Quality of evidence	Overall quality of evidence	Combination therapy with Anti-TNF and Methotrexate	Anti-TNF alone	Relative (95% CI)	Absolute (95% CI)	
Clinical Remission (Induction) (follow up: 12-14 weeks) (**CRITICAL** for decision making)							⊕⊖⊖⊖ **VERY LOW**					
2 RCTs[58, 59] *Adult population*	Serious [a]	Not serious [b]	Serious [c]	Very serious [d]	None	⊕⊖⊖⊖ **VERY LOW**		53/74 (71.6%) Infliximab + Methotrexate	51/71 (71.8%) Infliximab alone	RR 0.99 (0.82 to 1.20)	7 fewer per 1,000 (from 129 fewer to 144 more)	No statistically significant difference in clinical remission between Infliximab and Methotrexate vs. Infliximab alone.
Clinical Remission (Induction): (follow up: 26 weeks) (**IMPORTANT** for decision making)												
1 Observational Cohort study[57] *Pediatric population*	Serious [e]	Not serious	Serious [h]	Very serious [f]	None	⊕⊖⊖⊖ **VERY LOW**	⊕⊖⊖⊖ **VERY LOW**[l]	No statistically significant difference in clinical remission between Adalimumab and Immunomodulator (Azathioprine / Methotrexate) vs. Adalimumab alone (35.9% vs. 29.6%).				No statistically significant difference in clinical remission between Adalimumab and immunomodulator vs. Adalimumab alone.
Loss of Clinical Response (Maintenance) (follow up: 54 weeks) (**CRITICAL** for decision making)												
1 RCT[54] *Pediatric population*	Serious [g]	Not serious	Serious [h]	Very serious [d]	None	⊕⊖⊖⊖ **VERY LOW**		3/45 (4.4%) Infliximab + Azathioprine or Methotrexate	2/39 (5.1%) Infliximab alone	RR 0.87 (0.13 to 5.87)	7 fewer per 1,000 (from 45 fewer to 250 more)	No statistically significant difference in loss of clinical response between Infliximab and Azathioprine or Methotrexate vs. Infliximab alone.
Clinical Remission (Maintenance): (follow up: 48-50 weeks) (**CRITICAL** for decision making)												
2 RCTs[58, 59] *Adult population*	Serious [a]	Not serious [i]	Serious [c]	Very serious [d]	None	⊕⊖⊖⊖ **VERY LOW**		44/74 (59.5%)	40/71 (56.3%)	RR 1.12 (0.71 to 1.77)	68 more per 1,000 (from 163	No statistically significant difference in clinical remission between Infliximab

											fewer to 434 more)	and Methotrexate vs. Infliximab alone.
Clinical Remission (Maintenance): (follow up: 6 months) (**CRITICAL** for decision making)												
1 SR[55] (observational data from 2 RCTs) *Adult population*	Not serious	Not serious [h]	Very serious [c,h]	Serious [k]	None	⊕⊖⊖⊖ **VERY LOW**		40/71 (56.3%) Infliximab + Azathioprine or Methotrexate	68/165 (41.2%) Infliximab alone	OR 1.73 (0.97 to 3.07)	136 more per 1,000 (from 7 fewer to 271 more)	No statistically significant difference in clinical remission between Infliximab and immunomodulator vs. Infliximab alone.
Clinical Remission (Maintenance): (**CRITICAL** for decision making)												
1 SR (network meta-analysis)[52] *Adult population*	Serious [a]	Not serious	Serious [c]	Very serious [d]	None	⊕⊖⊖⊖ **VERY LOW**		OR 0.91 (0.41 to 2.1), 41% probability that Infliximab + Methotrexate is superior to Infliximab alone				No statistically significant difference in clinical remission between Infliximab and Methotrexate vs. Infliximab alone.
Adverse events (Maintenance): (follow up 52 weeks) (**IMPORTANT** for decision making)												
2 RCTs[58, 59] *Adult population*	Serious [a]	Not serious [b]	Serious [c]	Very serious [d]	None	⊕⊖⊖⊖ **VERY LOW**		Not calculable as only events were reported in the larger trial (not patients with events)				No statistically significant difference in adverse events between Infliximab and Methotrexate vs. Infliximab alone.

a. One trial had unclear risk of bias for allocation concealment, the other trial was open-label and unblinded. High risk for performance and detection bias.
b. No statistical heterogeneity ($I^2 = 0\%$)
c. Downgraded for indirectness. No pediatric data.
d. Downgraded for imprecision as the 95% CI crosses the clinical decision threshold between recommending and not recommending combination therapy (i.e. clinical action would differ if the upper versus the lower boundary of the CI represented the truth).
e. Subgroup analysis of the IMAgINE trial. Unclear whether prognostic factors are balanced.
f. Small sample size (n = 188) and low event rates (n = 63 clinical remission).
g. This trial was open-label and unblinded. High risk for performance and detection bias.
h. Downgraded for indirectness. The combination therapy arm includes either Azathioprine or Methotrexate, but it was unclear how many patients were on Methotrexate versus Azathioprine.
i. No statistical heterogeneity ($I^2 = 37\%$)
j. No statistical heterogeneity ($I^2 = 0\%$)
k. Small sample size (n = 236) and low event rates (n = 108).
l. Overall quality of evidence is anchored on efficacy and safety data in adult population with support of pediatric data.

Statement #23

Evidence for statement #23: In patients with Crohn's disease who have suboptimal clinical response to anti-TNF induction therapy or loss of response to maintenance therapy, we suggest regimen intensification informed by therapeutic drug monitoring.

PICO: In patients with Crohn's disease who have suboptimal clinical response to anti-TNF induction therapy or loss of response to maintenance therapy, should therapeutic drug monitoring vs. no therapeutic drug monitoring be used to guide regimen intensification (to increase the rates of clinical remission and reduce the rates of adverse events)?

Quality assessment								Summary of findings				Comments
								No of patients (ITT)		Effect		
Studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Quality of evidence	Overall quality of evidence	TDM	No TDM	Relative (95% CI)	Absolute (95% CI)	
Clinical Remission (Maintenance): (follow up: 1 year) (**CRITICAL** for decision making)							⊕⊖⊖⊖ **VERY LOW**[j]					
1 RCT[60] *Adult population*	Serious [a]	Not serious	Serious [b]	Very serious [c]	None	⊕⊖⊖⊖ **VERY LOW**		57/91 (62.6%)	45/82 (54.9%)	RR 1.14 (0.89 to 1.47)	77 more per 1,000 (from 60 fewer to 258 more)	No statistically significant difference in clinical remission between TDM vs. no TDM (subgroup data for patients with Crohn's disease)
Clinical Remission (Maintenance): (**CRITICAL** for decision making)												
3 SRs (observational studies)[61-63] *Adult population (mainly)*	Serious [d]	Serious [e]	Serious [b]	Serious [f]	Suspected publication bias based on funnel plot	⊕⊖⊖⊖ **VERY LOW**		Higher serum anti-TNF levels were associated with a greater probability of clinical remission. Antibodies to anti-TNFs were associated with greater likelihood of loss of response.				
Clinical Remission (Maintenance): (**CRITICAL** for decision making)												
2 cohort studies[64, 65] *Pediatric population*	Serious [d]	Serious [g]	Not serious	Serious [h]	None	⊕⊖⊖⊖ **VERY LOW**		Higher serum anti-TNF levels were associated with a greater probability of clinical remission. Antibodies to anti-TNFs were associated with greater likelihood of loss of response.				
Serious adverse events (Maintenance): (**IMPORTANT** for decision making)												
1 RCT[60] *Adult population*	Serious [a]	Not serious	Serious [b]	Very serious [i]	None	⊕⊖⊖⊖ **VERY LOW**		1/128 (0.8%)	0/123 (0%)	Not calculable		No statistically significant difference in adverse events between TDM vs. no TDM for patients with inflammatory bowel disease.

a. "Patients and treating physicians were blinded to individual Infliximab trough and antibodies to Infliximab (ATI) concentrations." However, during the maintenance phase, the interventions (dosing based on clinical features versus dosing based on TDM levels) cannot be blinded.
b. Downgraded for indirectness. No pediatric data.
c. Downgraded for imprecision as the 95% CI crosses the clinical decision threshold between recommending and not recommending TDM (i.e. clinical action would differ if the upper versus the lower boundary of the CI represented the truth).
d. Most included studies were considered high risk for selection bias and prognostic imbalance with residual confounding factors.
e. Significant statistical heterogeneity for all 3 cohort studies ($I^2 > 50\%$).
f. Most risk ratios (RR) are between 2 to 3 (not helpful as a diagnostic test).
g. Some inconsistency with respect to correlation between antibodies to anti-TNF therapy and remission / response.
h. Small sample size (n = 335) and low event rates.
i. Small sample size (n = 251) and low event rates (n = 1).
j. Overall quality of evidence is anchored on efficacy and safety data in adult population with support of pediatric data.

No consensus L

Evidence for No consensus L. In patients with Crohn's disease who have achieved a clinical remission with anti-TNF therapy, the consensus group does not make a recommendation (for or against) regarding assessment for mucosal healing within the first year to determine the need to modify therapy.

PICO: In patients with Crohn's disease who have achieved a clinical remission with anti-TNF therapy, should assessment for mucosal healing within the first year vs. no assessment for mucosal healing be done (to increase the rates of clinical remission and reduce the rates of adverse events)?

Quality assessment								Summary of findings				Comments
								No of patients (ITT)		Effect		
Studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Quality of evidence	Overall quality of evidence	Mucosal healing	No mucosal healing	Relative (95% CI)	Absolute (95% CI)	
Clinical Remission: relative to placebo (follow up: at least 50 weeks) (**CRITICAL** for decision making)												
1 SR (10 cohort studies)[45] *Adult and Pediatric population*	Very serious [a]	Not serious [b]	Very serious [c]	Serious [c]	None	⊕⊖⊖⊖ **VERY LOW**	⊕⊖⊖⊖ **VERY LOW** [e]	193/280 (68.9%)	131/308 (42.5%)	**OR 2.80 (1.91-4.10)**	**249 more per 1,000 (from 160 more to 327 more)**	Mucosal healing is associated with long-term clinical remission. Sensitivity analysis showed no difference in outcomes if mucosal healing was achieved on biologics vs. non-biologics.

f. Downgraded for risk of bias. Limited by potential residual confounding factors and selection bias.
g. No statistical heterogeneity ($I^2 = 0\%$)
h. Downgraded for indirectness. Mucosal healing is a surrogate outcome for patient important outcomes such as clinical remission, reduced risk of hospitalization or surgery. Observational data suggested that achieving mucosal healing is associated with improved clinical outcomes. Mucosal healing is therefore an important prognostic sign regarding disease course and response to treatment. However, no studies have compared the benefits and risks of achieving mucosal healing versus clinical remission alone or endoscopic remission alone. Also, serious variability with respect to participants (severity, phenotypes, duration of disease), concomitant medications, interventions used to assess mucosal healing, and timing of endoscopy or imaging studies. Included 3 pediatric studies.
i. Small sample size (n = 588).
j. Overall quality of evidence is anchored on data in adult population with support of pediatric data.

NON-ANTI-TNF BIOLOGICS

Statement #24

Evidence for statement #24: In patients with moderate to severe Crohn's disease who fail to achieve or maintain clinical remission with anti-TNF based therapy, we suggest ustekinumab to induce and maintain clinical remission.

PICO: In patients with moderate to severe Crohn's disease who fail to achieve or maintain clinical remission with anti-TNF based therapy, should ustekinumab vs. placebo / other treatments be used to induce and maintain clinical remission?

Quality assessment								Summary of findings				
								No of patients (ITT)		Effect		
Studies	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Quality of evidence**	**Overall quality of evidence**	**Ustekinumab**	**Placebo**	**Relative (95% CI)**	**Absolute (95% CI)**	**Comments**
Failure to induce Remission (Induction) (follow up: 6 weeks) (**CRITICAL** for decision making)							⊕⊕⊕⊖ **MODERATE**					
1 SR (4 RCTs)[66] *Adult population*	Not serious	Not serious [a]	Serious [b]	Not serious	None	⊕⊕⊕⊖ **MODERATE**		1049/1332 (78.8%)	539/615 (87.6%)	**RR 0.91 (0.86 to 0.95)**	**79 fewer per 1,000 (from 44 fewer to 123 fewer)**	Ustekinumab is superior to placebo for induction of clinical remission.
Clinical Remission (Maintenance): (follow up: 22 weeks) (**CRITCAL** for decision making)												
2 RCTs[67, 68] *Adult population*	Not serious	Not serious [c]	Serious [b]	Not serious	None	⊕⊕⊕⊖ **MODERATE**	⊕⊕⊕⊖ **MODERATE** [f]	161/329 (48.9%)	67/204 (32.8%)	**RR 1.44 (1.15 to 1.81)**	**145 more per 1,000 (from 49 more to 266 more)**	Ustekinumab is superior to placebo for maintenance of clinical remission.
Serious adverse events (Induction and Maintenance): (follow up 22 weeks) (**IMPORTANT** for decision making)												
2 RCTs[67, 68] *Adult population*	Not serious	Serious [d]	Serious [b]	Serious [e]	None	⊕⊖⊖⊖ **VERY LOW**		63/657 (9.6%)	26/265 (9.8%)	RR 1.11 (0.44 to 2.84)	11 more per 1,000 (from 55 fewer to 181 more)	No statistically significant difference in adverse events between Ustekinumab and placebo.

a. No significant statistical heterogeneity (I^2 = 27%).
b. Downgraded for indirectness. No pediatric data.
c. No significant statistical heterogeneity (I^2 = 0%)
d. Significant statistical heterogeneity (I^2 = 72%)
e. Downgraded for imprecision as the 95% CI crosses the clinical decision threshold between recommending and not recommending Ustekinumab (i.e. clinical action would differ if the upper versus the lower boundary of the CI represented the truth).
f. Overall quality of evidence is anchored on efficacy and safety data in adult population.

No Recommendation M

Evidence for No Recommendation M: In patients with moderate to severe Crohn's disease who fail to achieve or maintain clinical remission with an anti-TNF based therapy, the consensus group does not make a recommendation (for or against) regarding the use of vedolizumab to induce and maintain clinical remission.

PICO: In patients with moderate to severe Crohn's disease who fail to achieve or maintain clinical remission with an anti-TNF based therapy, should vedolizumab vs. placebo / other treatments be used to induce and maintain clinical remission?

Quality assessment								Summary of findings				Comments
Studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Quality of evidence	Overall quality of evidence	No of patients (ITT) Vedolizumab	No of patients (ITT) Placebo	Effect Relative (95% CI)	Effect Absolute (95% CI)	
Failure to induce Remission (Induction) (follow up: 6 – 10 weeks) (**CRITICAL** for decision making)							⊕⊖⊖⊖ **VERY LOW**					
2 SR (3 RCTs)[52, 69] *Adult population*	Not serious	Serious [a]	Serious [b]	Serious [c]	None			421/556 (75.7%)	364/413 (88.1%)	**RR 0.87 (0.79 to 0.95)**	**115 fewer per 1,000 (from 44 fewer to 185 fewer)**	Vedolizumab is superior to placebo for induction of clinical remission.
Clinical Remission (Maintenance): (follow up: 52 weeks) (**CRITCAL** for decision making)							⊕⊕⊖⊖ **LOW**					
2 SR (1 RCT)[52, 69] *Adult population*	Not serious	Not serious	Serious [b]	Serious [d]	None			116/308 (37.7%)	33/153 (21.6%)	**RR 1.75 (1.25 to 2.44)**	**162 more per 1,000 (from 54 more to 311 more)**	Vedolizumab is superior to placebo for maintenance of clinical remission.
Clinical Remission (Induction and Maintenance): (follow up: 6 and 22 weeks) (**IMPORTANT** for decision making)							⊕⊖⊖⊖ **VERY LOW** [h]					
1 case series[70] *Pediatric population*	Very Serious [e]	Not serious	Not serious	Serious [f]	None			Clinical remission was seen in 5.0% of patients with inflammatory bowel disease (both Crohn's and Ulcerative colitis) at week 6 and 20.0% by week 22. No comparator.				
Serious adverse events (Induction): (follow up 22 weeks) (**IMPORTANT** for decision making)							⊕⊕⊖⊖ **LOW**					
2 SR (3 RCTs)[52, 69] *Adult population*	Not serious	Not serious [g]	Serious [b]	Serious [c]	None			49/556 (8.8%)	35/413 (8.5%)	RR 0.97 (0.65 to 1.47)	3 fewer per 1,000 (from 30 fewer to 40 more)	No statistically significant difference in adverse events between Vedolizumab and placebo.

a. Significant statistical heterogeneity (I^2 = 51%).
b. Downgraded for indirectness. No pediatric data.
c. Downgraded for imprecision as the 95% CI crosses the clinical decision threshold between recommending and not recommending Vedolizumab (i.e. clinical action would differ if the upper versus the lower boundary of the CI represented the truth).
d. Small sample size (n = 461).
e. No comparator group. High risk for selection bias.
f. Very small sample size (n = 16 with Crohn's disease)
g. No significant statistical heterogeneity (I^2 = 0%)
h. Overall quality of evidence is anchored on efficacy and safety data in adult population with a paucity of pediatric data.

ALTERNATIVE THERAPIES

Statement #25

Evidence for statement #25: In patients with Crohn's disease, we recommend against cannabis or derivatives to induce or maintain remission.

PICO: In patients with Crohn's disease, should cannabis or derivatives vs. placebo / other treatments be used to induce and maintain clinical remission?

Quality assessment								Summary of findings				Comments
								No of patients (ITT)		Effect		
Studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Quality of evidence	Overall quality of evidence	Cannabis	Placebo	Relative (95% CI)	Absolute (95% CI)	
Clinical Remission (Induction) (follow up: 8 weeks) (**CRITICAL** for decision making)												
2 RCTs / 1 SR (1 RCT)[71-73] *Adult population*	Serious [a]	Not serious [b]	Serious [c]	Very serious [d]	None	⊕⊖⊖⊖ **VERY LOW**		9/21 (42.9%)	4/19 (21.1%)	RR 2.03 (0.74 to 5.56)	217 more per 1,000 (from 55 fewer to 960 more)	No statistically significant difference in clinical remission between Cannabis and placebo.
Adverse events: (**IMPORTANT** for decision making)												
1 cohort study[74] *Adult population*	Serious [e]	Not serious	Serious [f]	Very serious [g]	None	⊕⊖⊖⊖ **VERY LOW**	⊕⊖⊖⊖ **VERY LOW**	Use of Cannabis for more than 6 months at any time for IBD symptoms was a strong predictor of requiring surgery in patients with Crohn's disease (OR 5.0 (1.4 to 17.5).				
Side effects: (follow up: 8 weeks) (**IMPORTANT** for decision making)												
2 RCTs / 1 SR (1 RCT)[71-73] *Adult population*	Serious [a]	Not serious	Serious [c]	Very serious [d]	None	⊕⊖⊖⊖ **VERY LOW**		No statistically significant difference in side effects between Cannabis and placebo (measured on a scale of 1 to 7).				

a. Patients are unlikely to be truly blinded due to the effects of cannabis.
b. No statistically significant heterogeneity (I^2 = 28%)
c. Downgraded for indirectness. No pediatric data.
d. Downgraded for imprecision as the 95% CI crosses the clinical decision threshold between recommending and not recommending Cannabis (i.e. clinical action would differ if the upper versus the lower boundary of the CI represented the truth).
e. Imbalances in baseline characteristics and prognostic factors. Possible residual confounding factors. Selection bias as the cohort was a single-centered population in a tertiary referral center. Reporting bias may be present.
f. Downgraded for indirectness. No pediatric data. Included patients with Crohn's disease, ulcerative colitis, and indeterminate colitis.
g. Downgraded for imprecision. Small sample size (n = 42 Cannabis user with Crohn's disease). Due to cross-sectional design, the association between surgery and cannabis use could be reverse causation.

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