AGA LIVING CLINICAL PRACTICE GUIDELINE ON THE PHARMACOLOGIC MANAGEMENT OF MODERATE-TO-SEVERE CROHN'S DISEASE

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REVIEWING FOR POTENTIAL UPDATE
March 30, 2026

DECISION: After reviewing updated evidence, the guideline panel decided not to issue any new recommendations of amend any existing recommendations.

Acknowledgement: *We wish to thank Dr. Sunny Chung who helped execute AI-based title and abstract screening for the living update.*

STEPS

1. We reviewed focused questions that were previously identified by the panel as being in the “living mode” (**Table 1**). No new agent has received regulatory approval since the last version of the guideline (December 2025).

S#	Focused Question	PICO Question			
		Patients	**Intervention**	**Comparator**	**Critical Outcomes**
1. (Living)	In adult outpatients with moderate-to-severely active CD, what is the efficacy of TNF antagonists (infliximab, adalimumab, certolizumab pegol), vedolizumab, ustekinumab, upadacitinib, and IL-23 antagonists (risankizumab, mirikizumab, guselkumab), for induction and maintenance of remission?	Adult outpatients with moderate-to-severely active CD	• TNF antagonists (infliximab, adalimumab, certolizumab pegol) • Vedolizumab • Ustekinumab • Upadacitinib • IL-23 antagonists (risankizumab, mirikizumab, guselkumab)	Placebo	• Induction of clinical remission • Maintenance of clinical remission
2. (Living)	In adult outpatients with moderate-to-severely active CD who are **naïve to advanced therapies**, what is the comparative efficacy of infliximab, adalimumab, certolizumab pegol, vedolizumab, ustekinumab, upadacitinib, risankizumab, mirikizumab and guselkumab, for induction and maintenance of remission?	Adult outpatients with moderate-to-severely active CD who are naïve to advanced therapies	• Infliximab • Adalimumab • Certolizumab pegol • Vedolizumab • Ustekinumab • Upadacitinib • Risankizumab • Mirikizumab • Guselkumab	Placebo or another active comparator	• Induction of clinical remission • Maintenance of clinical remission
3 (Living)	In adult outpatients with moderate-to-severely active CD who **have been exposed to advanced therapies**, what is the comparative efficacy of infliximab, adalimumab, certolizumab pegol, vedolizumab, ustekinumab, upadacitinib, risankizumab, mirikizumab and	Adult outpatients with moderate-to-severely active CD who have been exposed to advanced therapies	• Infliximab • Adalimumab • Certolizumab pegol • Vedolizumab • Ustekinumab • Upadacitinib • Risankizumab • Mirikizumab	Placebo or another active comparator	• Induction of clinical remission • Maintenance of clinical remission •

	guselkumab for induction and maintenance of remission?		• Guselkumab		
4. (Living)	In adult outpatients with moderate-to-severely active CD, is combination therapy of TNF antagonists with an immunomodulator (thiopurines or methotrexate) superior to TNF monotherapy or immunomodulator monotherapy for induction and maintenance of remission?	Adult outpatients with moderate-to-severely active CD	Combination therapy with a TNF antagonist and an immunomodulator (thiopurines or methotrexate)	• TNF antagonist monotherapy • Immunomodulator monotherapy (thiopurines or methotrexate)	• Induction of clinical remission • Maintenance of clinical remission
5. (Living)	In adult outpatients with moderate-to-severely active CD, is combination therapy of a non-TNF biologic with an immunomodulator (thiopurines or methotrexate) superior to TNF monotherapy or immunomodulator monotherapy for induction and maintenance of remission?	Adult outpatients with moderate-to-severely active CD	Combination therapy with a non-TNF antagonist biologic and an immunomodulator (thiopurines or methotrexate)	• Non-TNF antagonist biologic monotherapy • Immunomodulator monotherapy (thiopurines or methotrexate)	• Induction of clinical remission • Maintenance of clinical remission
6. (Living)	In adult outpatients with moderate-to-severely active CD in steroid-free remission on combination therapy of TNF antagonist + immunomodulator, is discontinuation of (a) an immunomodulator or (b) discontinuation of a TNF antagonist, inferior to continuation of combination therapy?	Adult outpatients with moderate-to-severely active CD in steroid-free remission on combination therapy	• Discontinuation of an immunomodulator • Discontinuation of a biologic	Continuation of combination therapy	• Prevention of relapse

2. The evidence synthesis team conducted an updated literature search from **August 14, 2024 till March 11, 2026**, addressing these six focused questions. We searched MEDLINE, Embase, and Cochrane CENTRAL via Ovid. The search combined controlled vocabulary and text words related to UC, with validated RCT filters applied to MEDLINE and Embase. We excluded

pediatric studies and non-English language studies. The search identified **2,381 potential studies**. The search strategy is listed in the appendix.

3. The identified title/abstracts were then reviewed by the AGA's validated large language model pipeline (Chung *et al*. *Gastroenterology* 2025; doi: 10.1053/j.gastro.2025.03.034) for evidence synthesis for clinical guidelines. With this pipeline and after excluding duplicates, **252 articles were selected for further review**. Two guideline panel members (Siddharth Singh and Yuhong Yuan) reviewed these studies independently.
4. After review, one new RCT addressing PICO #6, was identified.

Study	Title	Abstract	DOI
Irving 2026 (Conference abstract)	Randomised controlled trial of withdrawal of thiopurines in patients with IBD switching from intravenous to subcutaneous infliximab: Results of the MINIMISE study	Background: Combining thiopurines (TP) with intravenous (IV) infliximab (IFX) decreases the rate of immunogenicity. Subanalyses of registration studies show that subcutaneous (SC) IFX may be associated with a decreased chance of developing anti-drug antibodies (ADAb) compared to IV IFX. However, there are no randomised controlled trials (RCT) to inform the decision of whether to continue or discontinue TP when switching from IV to SC. Method(s): We conducted a multicentre, RCT of TP withdrawal in patients switching from IV to SC IFX. Patients with IBD in stable remission (HBI <=4 or SCCAI <=2) who had been receiving IV IFX for at least 22 weeks at stable doses of up to 5mg/kg q4w or 10mg/kg q8w along with a TP were randomised to continue or discontinue the TP. Patients had therapeutic IFX drug levels (DL) at screening and were stratified by HLA DQA1*05 status. Primary outcome was the proportion of patients who developed free antidrug antibodies (ADAb) at week 24 (ie detectable antibodies in the absence of detectable drug). Using a non-inferiority design to detect a 15% difference, 102 patients were required to meet the target of 88 evaluable patients at week 24. Result(s): 102 patients (63=CD, 39=UC, 5=IBD-U) were randomised (Table 1). For the primary outcome, detection of free ADAb at 24W, 88 patients were evaluable (2 patients withdrew early, 8 patients attended outside 1 week window for week 24 assessment, 4 patients did not provide week 24 samples). TP withdrawal was non inferior to continuation (difference-2.4 (95% CI:-12.3 to 5.4) P = 0.46). 1/41 patients in the stop group developed free ADAb compared with 0/47 in the continue group; a sensitivity analysis including the samples from the early withdrawal patients and the patients who provided late samples at week 24, none of whom developed free ADAb, did not change the outcome. HLA DQA1*05 status did not affect IFX DL, nor free or total ADAb formation. Median IFX levels (ug/ml) at weeks 8, 16 and 24 were 15.5, 17.7 and 18.4 in the continue arm vs 17.0, 15.5 and 15.1 in the stop arm. The proportion of patients with total positive ADAb at the same time points was 21%, 22% and 20% (continue) and 12%, 15% and 18% (stop). There was no difference at week 24 in clinically active disease (HBI >4, SCCAI>2), biomarker activity (FC > 250 ug/g or CRP >5 mg/L) or combined clinical and biomarker activity (Figure 1). One patient reverted to IV IFX (stop group), one patient required admission for pneumonia and one patient developed a basal cell carcinoma (both continue group). Conclusion(s): IBD patients in stable remission on combination therapy with IV IFX and TP can be safely switched to SC IFX without the need for continuation of the thiopurine to prevent ADAb.	https://academic.oup.com/ecco-jcc/article/20/Supplement_1/jjaf231.145/8432457

5. The guideline panel reviewed this information virtually on March 30, 2026

6. On reviewing the new evidence in the context of existing evidence and recommendations, the panel determined that new evidence was unlikely to meaningfully change the certainty of evidence that informed prior recommendations. The panel determined that new evidence did NOT warrant a change in existing recommendations or need for new recommendation statements.

Appendix:

Search strategy

From 20240814-20260311

(conference abstracts are kept)

N=2381 (split in two files: 1-1500; 1501-2381

Ovid MEDLINE(R) ALL <1946 to March 10, 2026>
Embase <1974 to 2026 March 09>
EBM Reviews - Cochrane Central Register of Controlled Trials <January 2026>

1 Crohn Disease/ use medall,cctr 50963
2 exp Crohn disease/ use oemezd 135687
3 Crohn*.ti,ab,kw,kf,af. 247700
4 ((Inflammatory bowel disease* or IBD) not (ulcerative colitis or UC)).ti. 114535
5 or/1-4 [CD] 289558
6 exp Tumor Necrosis Factor Inhibitors/ use medall,cctr 22879
7 exp tumor necrosis factor antibody/ use oemezd 12523
8 exp Receptors, Tumor Necrosis Factor/ use medall,cctr 56861
9 exp Tumor Necrosis Factors/ use medall,cctr 185699
10 tumor necrosis factor/ use oemezd 510598
11 tumor necrosis factor receptor/ use oemezd 13127
12 ((tumor necrosis or tumour necrosis or TNF or antitumor necrosis or antitumour necrosis or antiTNF* or Cachectin) adj2 (factor* or inhibit* or antibod* or antagonist* or block* or biologic*)).ti,ab,kw,kf. 469160
13 exp Antibodies, Monoclonal/ use medall,cctr 327192
14 exp monoclonal antibody/ use oemezd,medall,cctr 1304988
15 (monoclonal adj2 antibod*).ti,ab,kw,kf. 545462

16 (Infliximab or "ABP 710" or ABP710 or Avakine or Avsola or cA2 or Flixabi or "GP 1111" or GP1111 or IFX or Inflectra or INFLIX or Ixifi or "PF 06438179" or "PF 6438179" or PF06438179 or PF6438179 or Remicade or Remsima or Renflexis or Revellex or "TA 650" or TA650 or Zessly or "MAb cA2" or "170277‐31‐3").ti,ab,kw,kf,rn. 387804
17 (Adalimumab or Humira or Amjevita or Cyltezo or "D2E7 Antibody" or Trudexa or "abp 501" or abp501 or "abt d2e7" or abtd2e7 or adaly or amgevita or "avt 02" or avt02 or "bat 1406" or bat1406 or "bax 2923" or "bax 923" or bax2923 or bax923 or "bi 695501" or bi695501 or "chs 1420" or chs1420 or "ct p17" or ctp17 or "da 3113" or da3113 or "dmb 3113" or dmb3113 or exemptia or "fkb 327" or fkb327 or fyzoclad or "gp 2017" or gp2017 or hadlima or halimatoz or hefiya or "hlx 03" or hlx03 or hulio or hyrimoz or "ibi 303" or ibi303 or idacio or imraldi or kromeya or "lu 200134" or lu200134 or "m 923" or m923 or mabura or "msb 11022" or msb11022 or "ons 3010" or ons3010 or "pf 06410293" or "pf 6410293" or pf06410293 or pf6410293 or raheara or "sb 5" or sb5 or solymbic or "zrc 3197" or zrc3197 or "1446410‐95‐2" or "331731‐18‐1").ti,ab,kw,kf,rn. 75391
18 (Certolizumab or "cdp 870" or cdp870 or cimzia or "pha 738144" or pha738144 or "428863‐50‐7").ti,ab,kw,kf,rn. 14616
19 (Vedolizumab or anti alpha 4* or antialpha 4* or Entyvio or kynteles or "idp 02" or idp02 or "MLN 02" or mln02 or "MLN‐0002" or MLN0002 or "pb 016" or pb016 or ro7246311 or "ro 7246311").ti,ab,kw,kf,rn. 16405
20 (Natalizumab or "an 10022" or "an 100226" or an10022 or "an100226" or antegran or antegren or "bg 0002" or bg0002 or "dst 356a1" or dst356a1 or "pb 006" or pb006 or "pbp 2002" or pbp2002 or tyruko or tysabri).ti,ab,kw,kf,rn. 20717
21 (Ustekinumab or "abp 654" or abp654 or "avt 04" or avt04 or "bat 2206" or bat2206 or "bfi 751" or bfi751 or "bmab 1200" or bmab1200 or "bow 090" or bow090 or "cnto 1275" or cnto1275 or "ct p43" or ctp43 or "dmb 3115" or dmb3115 or "eb 1004" or eb1004 or "fyb 202" or fyb202 or "ons 3040" or ons3040 or "pb 007" or pb007 or "ro 723 3920" or "ro 7233920" or ro7233920 or "sb 17" or sb17 or stelara or stellara).ti,ab,kw,kf,rn. 24436
22 Janus Kinase Inhibitors/ use medall,cctr 3106
23 exp Janus kinase inhibitor/ use oemezd 51102
24 ((JAK or Janus Kinase or Janus tyrosine kinase) adj2 (antagonist* or inhibit* or block*)).ti,ab,kw,kf. 33264
25 (upadacitinib or "abt 494" or abt494 or rinvoq).ti,ab,kw,kf,rn. 9316
26 ((IL-23 or interleukin or cytokine) adj2 (antagonist* or inhibit* or block*)).ti,ab,kw,kf. 38223
27 exp cytokine receptor antagonist/ use oemezd 212889
28 (risankizumab or "abbv 066" or abbv066 or "bi 655066 bi655066" or skyrizi).ti,ab,kw,kf,rn. 4906
29 (mirikizumab or "ly 3074828" or ly3074828 or omvoh).ti,ab,kw,kf,rn. 1550
30 (guselkumab or "cnto 1959" or cnto1959 or tremfya).ti,ab,kw,kf,rn. 6176
31 (mercaptopurine or 6MP or "6‐MP" or allmercap or bw 57 323h or bw 57323h or bw57323h or empurine or e7wed276i5 or hanixol or ismipur or leukerin or leupurin* or loulla or medipurin or mercaleukin or mercaptopurine* or mercapurene or mern or mycaptine or nsc 755 or nsc755 or pkk6muz20g or puri nethol or purimmun or purine 6 thiol or purine thiol or purimethol or puri-nethol or purinethiol or purinethol or purixan or thiohypoxanthine or thiopurine* or u 4748 or u4748 or xaluprine).ti,ab,kw,kf,rn. 49411

32 exp Mercaptopurine/ use medall,cctr 22721
33 6 mercaptopurine derivative/ or mercaptopurine/ use oemezd 32500
34 (azathioprine or arathioprin* or aza-q or azafalk or azafor or azahexal or azamedac or azamun* or azanin or azapin or azapress or azaprine or azarex or azasan or azathiodura or azathiopine or azathioprim or azathioprin* or azathropsin or azatioprina or azatox or azatrilem or azopi or azoran or azothioprin* or azothioprine or am94r510ms or bw 57 322 or bw 57322 or bw57-322 or bw57322 or colinsan or immuran or immurel or immuthera or imunen or imuprin or Imuran* or imurek or imurel or imuren or jayempi or mrk240iy2l or nsc 39084 or nsc39084 or oraprine or ozathuia or Thioazeprine or thioprine or transimune or zytrim).ti,ab,kw,kf,rn. 154300
35 Methotrexate/ use medall,cctr 48560
36 methotrexate derivative/ or methotrexate/ use oemezd 240485
37 (Methotrexate or abitrexate or adx 2191 or adx2191 or amethopterin or amethopterine or ametopterine or antifolan or biotrexate or brimexate or canceren or cl 14377 or cl14377 or emt 25299 or emt25299 or emtexate or emthexat* or emtrexate or enthexate or farmitrexat* or farmotrex or folex or ifamet or imeth or jylamvo or lantarel or ledertrexate or lumexon or maxtrex or metatrexan or metex or methoblastin or methohexate or methotrate or methotrexate* or methylaminopterin* or metical or metoject or metothrexat* or metotrexat* or metotrexin or metrex or metrotex or mexate or mpi 2505 or mpi 5004 or mpi2505 or mpi5004 or MTX or neotrexate or nordimet or novatrex or nsc 740 or nsc740 or otrexup or r 9985 or r9985 or rasuvo or reditrex or reumatrex or texate or texorate or tremetex or trexall or trexeron or wr 19039 or wr19039 or xaken xatmep or zexate or zlatal).ti,ab,kw,kf,rn. 332428
38 (S1P receptor modulator* or Sphingosine-1-phosphate receptor modulator* or ozanimod or etrasimod or Amiselimod).ti,ab,kw,kf. 3907
39 (small molecul* or biologics or biologicals or ((biological or biologic) and (agent* or product* or drug*))).ti. 101625
40 (immunomodulator* or ((immunomodulating or immunotherapeutic) and (agent* or drug* or product*))).ti. 34619
41 or/6-40 [interventions of interest] 3178919
42 5 and 41 [CD and interventions] 87871
43 limit 42 to yr="2024 -Current" [CD and drugs after 2024] 12890
44 exp randomized controlled trial/ or controlled clinical trial.pt. or clinical trials as topic/ or (random* or placebo).ab. or trial.ti. 6789239
45 (exp animals/ not humans/) use medall 5432505
46 44 not 45 use medall [MEDLINE RCT filter] 6618494
47 43 and 46 use medall [RCTs in MEDLINE] 424
48 Randomized controlled trial/ or Controlled clinical study/ or randomization/ or intermethod comparison/ or double blind procedure/ or human experiment/ or (random$ or placebo or (open adj label) or ((double or single or doubly or singly) adj (blind or blinded or blindly)) or parallel group$1 or crossover or cross over or ((assign$ or match or matched or allocation) adj5 (alternate or group$1 or intervention$1 or patient$1 or subject$1 or participant$1)) or assigned or allocated or (controlled adj7 (study or design or

trial)) or volunteer or volunteers).ti,ab. or (compare or compared or comparison or trial).ti. or ((evaluated or evaluate or evaluating or assessed or assess) and (compare or compared or comparing or comparison)).ab. 14271142
49 (random$ adj sampl$ adj7 ("cross section$" or questionnaire$1 or survey$ or database$1)).ti,ab. not (comparative study/ or controlled study/ or randomi?ed controlled.ti,ab. or randomly assigned.ti,ab.) 22714
50 Cross-sectional study/ not (exp randomized controlled trial/ or controlled clinical study/ or controlled study/ or randomi?ed controlled.ti,ab. or control group$1.ti,ab.) 1066656
51 (((case adj control$) and random$) not randomi?ed controlled).ti,ab. 46857
52 Systematic review.ti,ab. not (trial or study).ti. 839082
53 (nonrandom$ not random$).ti,ab. 42034
54 "random field$".ti,ab. 7042
55 (random cluster adj3 sampl$).ti,ab. 3413
56 (review.ab. and review.pt.) not trial.ti. 2748005
57 "we searched".ab. and (review.ti. or review.pt.) 106909
58 "update review".ab. 285
59 (databases adj4 searched).ab. 155078
60 (rat or rats or mouse or mice or swine or porcine or murine or sheep or lambs or pigs or piglets or rabbit or rabbits or cat or cats or dog or dogs or cattle or bovine or monkey or monkeys or trout or marmoset$1).ti. and animal experiment/ 1344807
61 Animal experiment/ not (human experiment/ or human/) 2852705
62 or/49-61 7516709
63 48 not 62 use oemezd [Embase RCTs filler] 13323617
64 43 and 63 use oemezd [Embase RCTs] 2832
65 limit 47 to dt=20240814-20260311 use medall [Limit not valid in CCTR,Embase; records were retained] 282
66 limit 47 to ed=20240814-20260311 use medall [Limit not valid in CCTR,Embase; records were retained] 246
67 limit 64 to dd=20240814-20260311 use oemezd [Limit not valid in CCTR,Ovid MEDLINE(R); records were retained] 2244
68 limit 64 to dc=20240814-20260311 use oemezd [Limit not valid in CCTR; records were retained] 2284
69 47 and (2025* or 2026*).ep. 156
70 43 use cctr 557
71 or/65-70 [CD interventions from July 2024 three databases] 3164
72 limit 71 to english language 3142
73 (child/ or Pediatrics/ or Adolescent/ or Infant/ or adolescence/ or newborn/) not (adult/ or aged/) 5128766
74 72 not 73 3043
75 (baby or babies or child or children or pediatric* or paediatric* or peadiatric* or infant* or infancy or neonat* or newborn* or new born* or adolescen* or preschool or pre-school or toddler*).ti. not (adult* or elder* or senior* or men or women).tw. 3328579

76	74 not 75	2982
77	trial registry record.pt.	607243
78	"clinicaltrials.gov.".so.	553484
79	76 not (77 or 78)	2864
80	remove duplicates from 79	2381