Βέλτιστη διαχείριση ασθενών με ΙΦΝΕ

Σπύρος Σιακαβέλλας

Ηπατογαστρεντερολογική Μονάδα, Β' Παθολογική Πανεπιστημιακή Κλινική, ΓΝΑ Ιπποκράτειο

Δήλωση συμφερόντων

- **Αμοιβή ως ομιλητής σε εκπαιδευτικές ημερίδες από τις Janssen και Pfizer**

Εμβόλια - Πότε, ποια και σε ποιους;

Journal of Crohn's and Colitis, 2021, 879–913
doi:10.1093/ecco-jcc/jjab052
Advance Access publication March 17, 2021
ECCO Guideline/Consensus Paper

OXFORD

JCC
JOURNAL of CROHN'S and COLITIS

ECCO Guideline/Consensus Paper

ECCO Guidelines on the Prevention, Diagnosis, and Management of Infections in Inflammatory Bowel Disease

T. Kucharzik,[a] P. Ellul,[b] T. Greuter,[c] J. F. Rahier,[d] B. Verstockt,[e] C. Abreu,[f] A. Albuquerque,[g] M. Allocca,[h] M. Esteve,[i] F. A. Farraye,[j] H. Gordon,[k] K. Karmiris,[l] U. Kopylov,[m] J. Kirchgesner,[n] E. MacMahon,[o] F. Magro,[p] C. Maaser,[q] L. de Ridder,[r] C. Taxonera,[s] M. Toruner,[t] L. Tremblay,[u] M. Scharl,[v] N. Viget,[w] Y. Zabana,[i] S. Vavricka[v]; on behalf of the European Crohn's and Colitis Organisation [ECCO]

Table 4. Suggested time frame between stopping immunosuppressants and live vaccination, considering drug elimination half-life.[2,218,429–432]

Drug	Elimination half-life	Stopping before live vaccines	Restart after live vaccines
Steroids [prednisone] >1 mg/kg, >14 days [children] >20 mg/day, >14 days [adults]	2–3 h	1 month	1 month
Thiopurines[a] [azathioprine and 6-MP[b]: approximately 2 h]	Several days [6-TGN[c]]	3 months	1 month
Methotrexate, low dose [adults]	3–10 h	1 month	1 month
Tofacitinib	3 h	1 month	1 month
Infliximab	7–12 days	3 months	1 month
Adalimumab	Approximately 2 weeks	3 months	1 month
Golimumab	Approximately 2 weeks	3 months	1 month
Certolizumab	Approximately 2 weeks	3 months	1 month
Cyclosporine[d,e]	8.4 h [10–27]	1 month	1 month
Tacrolimus[e]	23–46 h	1 month	1 month
Vedolizumab[f]	25 days	3–4 months	1 month
Ustekinumab	Approximately 19 days	3 months	1 month

[a]Zoster live vaccine [ZVL] administration is considered safe with low-dose methotrexate [≤0.4 mg/kg/week] and azathioprine [≤3.0 mg/kg/day] or 6-mercaptopurine [≤1.5 mg/kg/day].

[b]6-MP: 6-mercaptopurine.

[c]6-TGN: 6-thioguanine nucleotides.

[d]Ciclosporin modified.

[e]Immediate-release formulations

[f]Vedolizumab is gut selective. The period of 3–4 months for stopping the drug before administration of a live vaccine may be lengthy, but further information is currently unavailable. The stopping period should be discussed on a case-by-case basis.

Table 5. Adult immunisation schedule for patients with IBD.

	Dosing, schedule, and remarks	Type of vaccine[a]	At diagnosis	At diagnosis and during follow-up	Strongly recommended before immunosuppressive treatment
IBD-specific vaccination programme					
Inactivated influenza [trivalent/quadrivalent or high dose]	Annual vaccination recommended for all patients on immunosuppressive therapy, according to national guidelines	Non-live		Yes	Yes
Zoster recombinant [RZV] [preferred]	For all patients ≥50 years. Consider in patients <50 years at increased risk of herpes zoster infection	Non-live			Yes
Zoster live [ZVL]	Use only if RZV is unavailable and patient is immunocompetent	Live-attenuated vaccine			Yes
Pneumococcal conjugate 13-valent [PCV13] and polysaccharide 23-valent [PPSV23]	Single dose of PCV13 followed by PPSV23 after 8 weeks, and a PPSV23 booster after 5 years. Additional PPSV23 booster according to national guidelines. If PPSV23 provided first, then administer a single dose of PCV13 after 1 year and a PPSV23 booster after 5 years. Additional PPSV23 booster according to national guidelines	Non-live	Yes	Yes	Yes
Hepatitis A [Hep A][b]	Consider hepatitis A vaccination. Schedule and dosage according to national guidelines	Non-live		Yes	
Human papillomavirus [HPV]	Two or three doses depending on age, for unvaccinated patients, both sexes	Non-live	Yes	Yes	
Hepatitis B [Hep B][c]	Three-dose series. Additional booster might be necessary according to level of seroprotection. Titres should be regularly checked	Non-live	Yes	Yes	Yes

Routine vaccination programme					
Tetanus, diphtheria, pertussis [Tdap or Td]	If previously immunised, single dose of Tdap, then Td or Tdap every 10 years according to national guidelines	Non-live	Yes	Yes	
Meningococcal vaccines[d]	For patients at high risk of invasive meningococcal disease. Schedule and dosage according to national guidelines	Non-live	Yes	Yes	
Measles, mumps, rubella [MMR]	Adults without evidence of immunity should receive 2 doses separated by at least 28 days	Live-attenuated vaccine	Yes		Yes
Varicella	Two doses 4–8 weeks apart only in patients with no history of chickenpox or shingles, no previous immunisation, and negative serology for varicella zoster	Live-attenuated vaccine	Yes		Yes
Poliomyelitis [inactivated parenteral poliovirus]	Schedule and dosage according to national guidelines	Non-live	Yes	Yes	
SARS-CoV-2	Schedule and dosage according to national guidelines	Non-live	Yes		Yes

IBD, inflammatory bowel disease.

[a]Live-attenuated vaccines are generally contraindicated for patients on immunosuppressive therapy.

[b]Indications for hepatitis A vaccination vary by region; in many countries this is only necessary before travel to endemic areas.

[c]ECCO supports the WHO goal to eliminate hepatitis B infection, and the WHO recommends that each region develop their own vaccination goals appropriate to their epidemiological situation in addition to routine vaccination following birth.[205] As such, hepatitis B immunisation should be considered in non-immune IBD patients, subject to regional policies.

[d]Not routinely used in adult patients with IBD unless a risk factor for invasive meningococcal disease is present; in paediatric patients, vaccines are administered according to national guidelines and routinely used if risk factors are present.

Πίνακας 2. Εθνικό Πρόγραμμα Εμβολιασμών Ενηλίκων, ανά νόσο ή άλλη ένδειξη, 2023

Εμβόλιο ▼	Κύηση ή λοχεία	Ανοσοκαταστολή (πλην HIV)	Λοίμωξη με HIV (CD4+ κύτταρα)		Ασπληνία, μόνιμη έλλειψη τελικών κλασμάτων συμπληρώματος	Νεφρική ανεπάρκεια τελικού σταδίου σε αιμοδιύλιση	Χρόνιες καρδιοπάθειες, πνευμονοπάθειες, κάπνισμα, χρόνιος αλκοολισμός,	Χρόνιες παθήσεις του ήπατος	Σακχαρώδης διαβήτης	Υγειονομικό προσωπικό	MSM
			<200	≥200							
[1] Γρίπης	1 δόση ετησίως										
[2] Tdap ή Tdap-IPV ή Td	1 δόση Tdap σε κάθε κύηση	Μία δόση Tdap ή Tdap-IPV και στη συνέχεια αναμνηστική δόση Td ή Tdap κάθε 10 χρόνια									
[3] MMR	Αντενδείκνυται			1-2 δόσεις δείτε σχόλιο							
[4] VAR	Αντενδείκνυται			2 δόσεις							
[5] HZV (ZVL)	Αντενδείκνυται				1 δόση						
[5] HZV (RZV)		2 δόσεις σε ηλικίες α)> 18 ετών με δύο ή περισσότερα έρπητα ζωστήρα, και β)> 60 ετών									
[6] HPV γυναίκες	Δεν συστήνονται δείτε σχόλιο	3 δόσεις μέχρι την ηλικία των 26 ετών									
[6] HPV άνδρες		3 δόσεις μέχρι την ηλικία των 26 ετών									3 δόσεις μέχρι 26 ετών
[7] PCV20		1 δόση PCV20								1 δόση PCV20	
[8] HepA		2 δόσεις	2 δόσεις		2 δόσεις			2 δόσεις	2 δόσεις		2 δόσεις
[9] HepB	3 δόσεις	3 ή 4 δόσεις δείτε σχόλιο									
[10] MenACWY	1 ή περισσότερες δόσεις ανάλογα με τις ενδείξεις δείτε σχόλιο										
[11] MenB		2-3 δόσεις δείτε σχόλιο			2-3 δόσεις δείτε σχόλιο					2-3 δόσεις ανάλογα με το εμβόλιο*	
[12] Hib		Σε μεταμόσχευση αιμοποιητικών κυττάρων χορηγούνται 3 δόσεις ανεξαρτήτως προηγηθέντος εμβολιασμού	1 δόση		1 δόση	1 δόση					

Συστήνονται για ενήλικες που πληρούν το ηλικιακό κριτήριο και δεν έχουν αποδεικτικό προηγούμενου εμβολιασμού ή νόσησης

Συστήνονται για ενήλικες με πρόσθετους παράγοντες κινδύνου ή άλλες ενδείξεις

Καθυστέρηση του εμβολιασμού έως την ολοκλήρωση της κύησης εάν ενδείκνυται το εμβόλιο

Αντενδείκνυται

Δεν συστήνονται

* Συστήνεται για το προσωπικό μικροβιολογικών εργαστηρίων που είναι δυνατόν να εκτεθεί σε καλλιέργειες μηνιγγιτιδοκόκκου

Βέλτιστη χρήση καλπροτεκτίνης κοπράνων

Χρήση καλπροτεκτίνης κοπράνων

- Αρχική διάγνωση (διάκριση μεταξύ ΙΦΝΕ και λειτουργικών συνδρόμων)
- Παρακολούθηση ενεργότητας νόσου
- Ανταπόκριση στη θεραπευτική αγωγή
- Πρόβλεψη υποτροπής
- Πρόβλεψη μετεγχειρητικής επανεμφάνισης (σε νόσο Crohn)

Treat to target

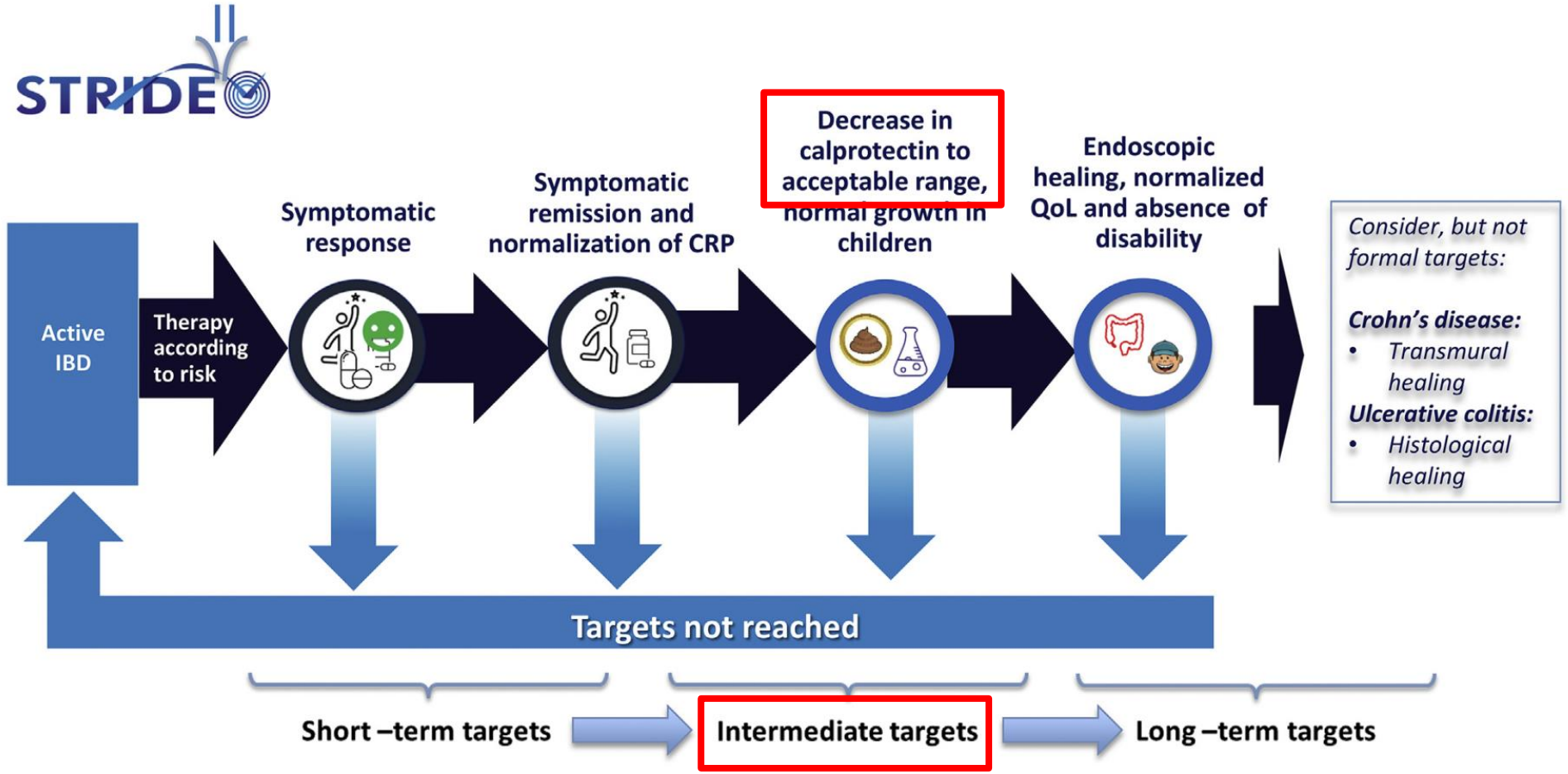
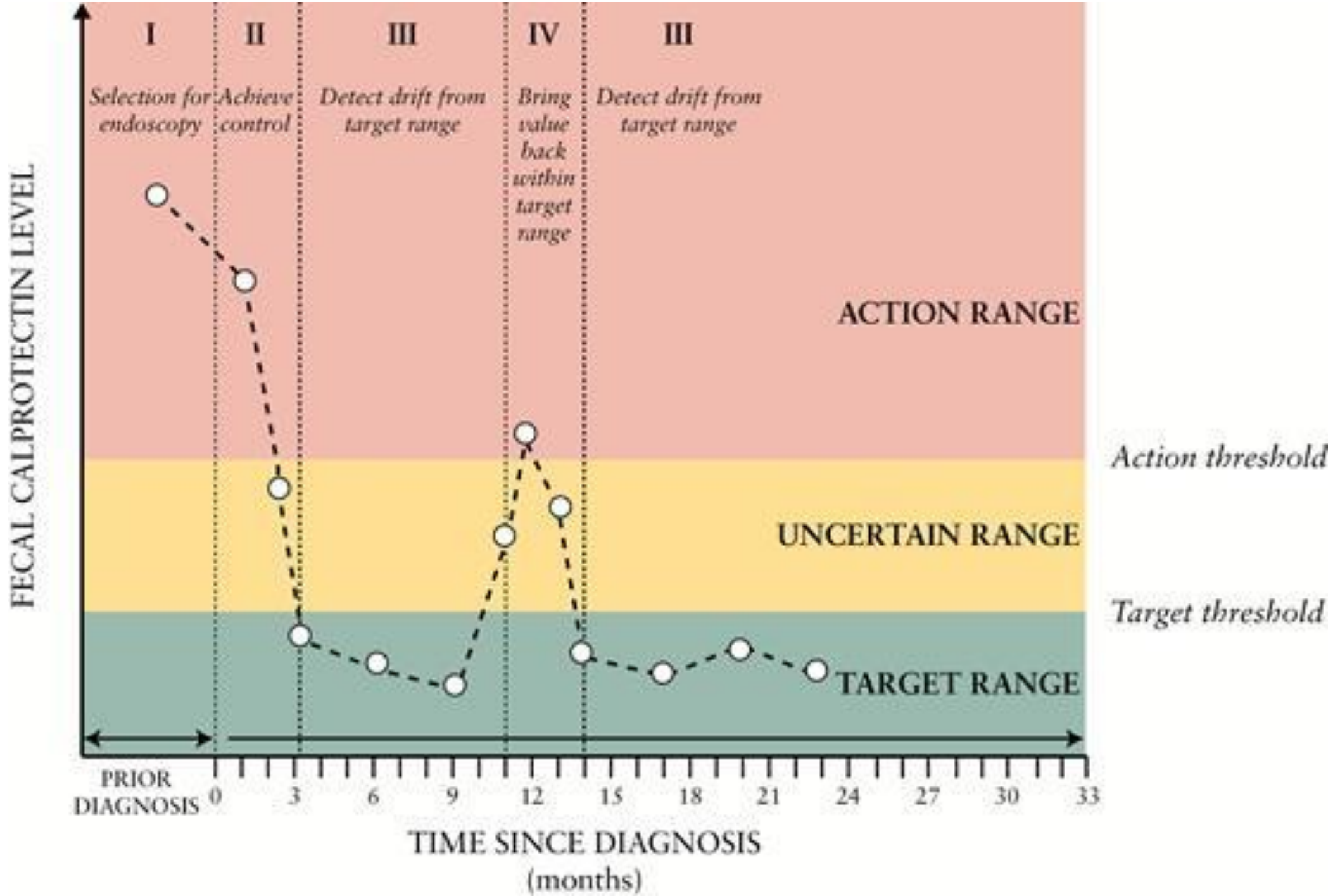
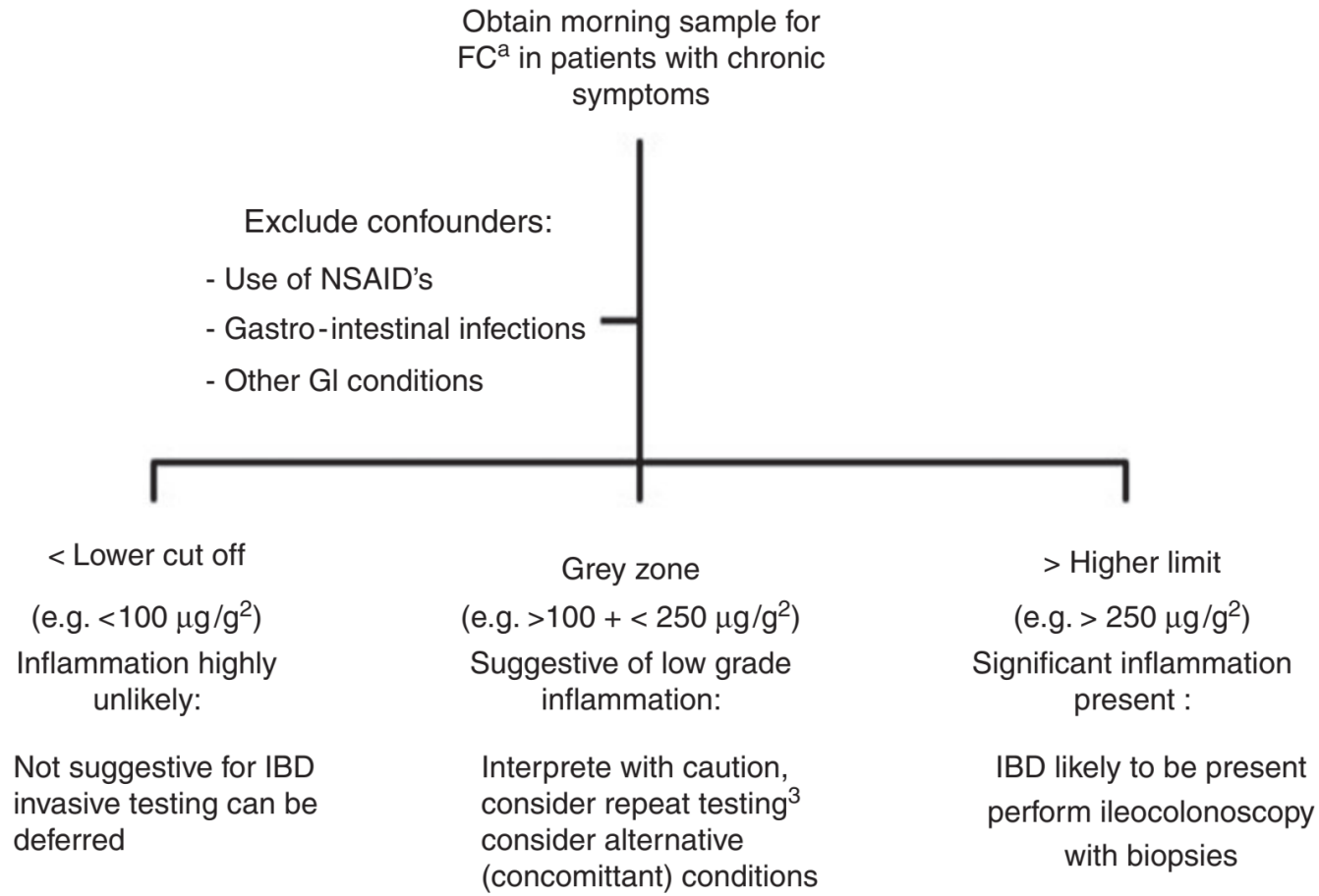


Figure 2. Treatment targets in CD and UC.

Turner, 2021, Gastroenterology


I
II
III
IV
III
Selection for endoscopy
Achieve control
Detect drift from target range
Bring value back within target range
Detect drift from target range
ACTION RANGE
UNCERTAIN RANGE
TARGET RANGE
Action threshold
Target threshold
FECAL CALPROTECTIN LEVEL
PRIOR DIAGNOSIS
0
3
6
9
12
15
18
21
24
27
30
33
TIME SINCE DIAGNOSIS
(months)

Διάγνωση ΙΦΝΕ



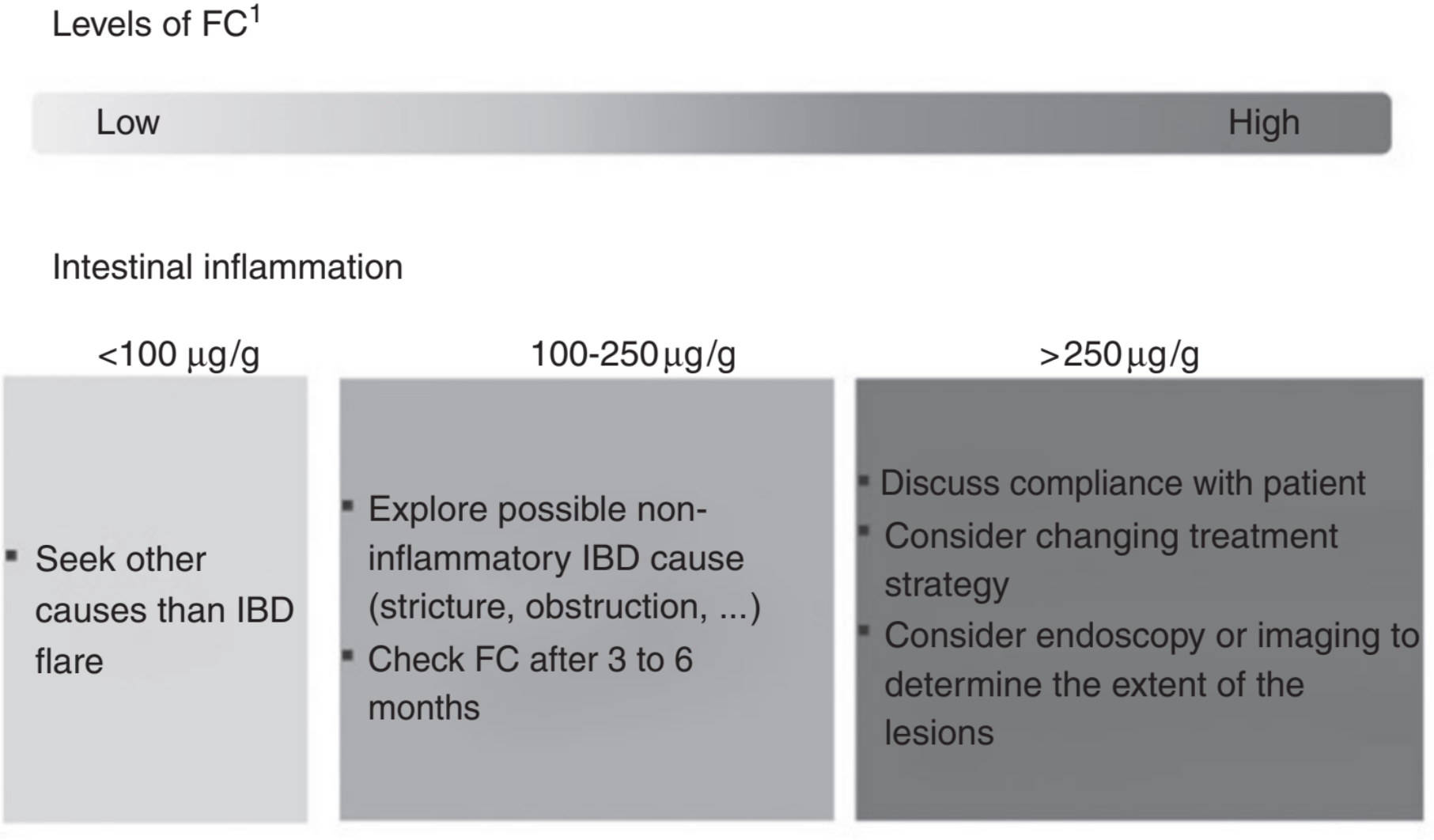
a: Different assays techniques are used without good international standardization

b: Optimal cut-offs may differ from assay to assay. Consult the manufacturer and literature on your test.

c: It is advised to use the same test in the follow-up of an individual patient to allow for optimal comparison.

Reenaers, 2018, UEGJ

Συμπτωματικοί ασθενείς



1 Use prior FC value of a particular patient if available for comparison and for correlation with endoscopic disease activity.

Reenaers, 2018, UEGJ

Ασυμπτωματικοί ασθενείς

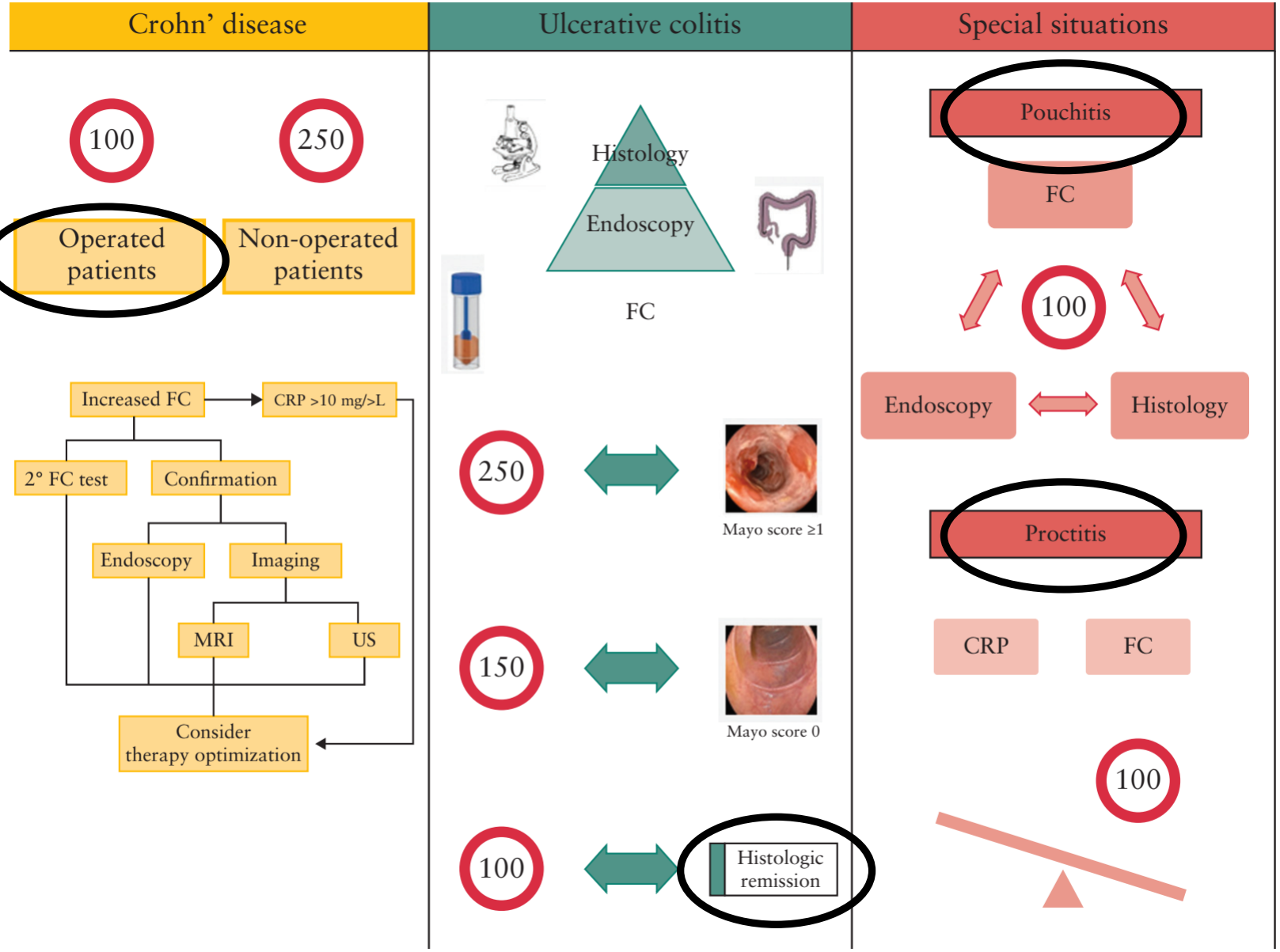
FC <100 μg/g	FC 100-250 μg/g	FC > 250 μg/g*
Mucosal and histological remission is likely	Residual inflammation likely	Significant inflammation still present
Flare up very unlikely	Compare with previous value	Flare in the coming months is likely
Continue therapy or consider deescalation	Plan for retesting at regular interval (s)	Complications may occur without therapeutic change Consider morphologic assessement (endoscopy and/or MRI) and optimize/change therapy

*CD: Sensitivity 61%, specificity 80%; UC: sensitivity 71%, specificity: 100%

1. Regular testing, e.g. at diagnosis, for monitoring, or at time of major therapeutic changes, will allow for comparison within an individual patient.

Reenaers, 2018, UEGJ

Ειδικές περιπτώσεις



D'Amico, 2021, JCC

Συμπεράσματα

- Καλπροτεκτίνη → σημαντικό εργαλείο στη διαγνωστική μας φαρέτρα και πλέον **θεραπευτικός στόχος**

- Τυποποίηση των τεχνικών μέτρησης είναι απαραίτητη

- Έλλειψη συγκεκριμένης τιμής cut-off → επιλογή πρέπει να συνεκτιμά κλινικό σενάριο
- Χαμηλότερες τιμές cut-off (50-100 μg/g) σε αρχική διάγνωση και μετεγχειρητικά
- Υψηλότερες τιμές (200-250 μg/g) σε γνωστή νόσο για παρακολούθηση και θεραπευτικές αποφάσεις

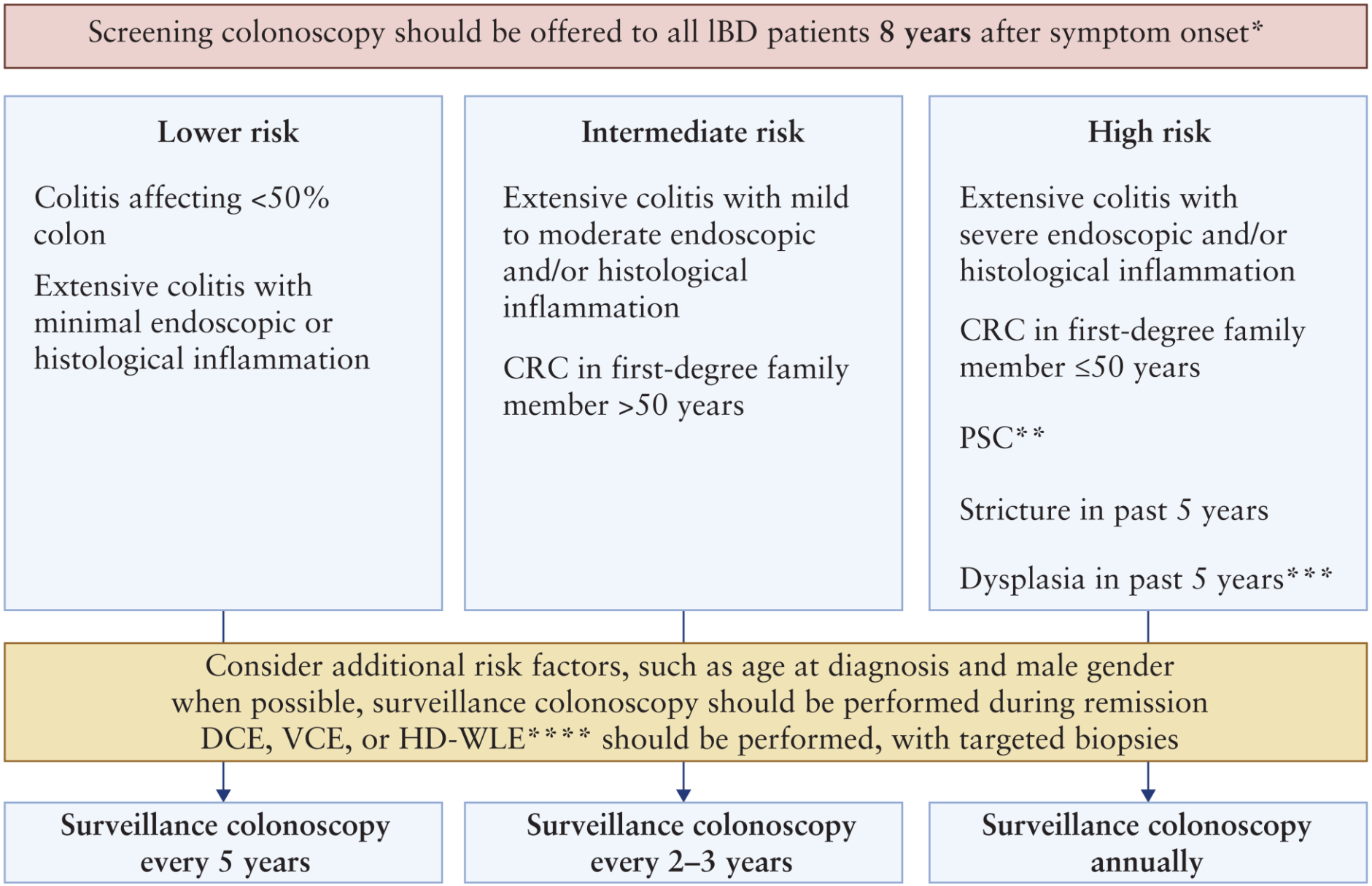
- **Όχι μεμονωμένη χρήση αλλά συμπληρωματική → συνδυασμός με κρίση θεράποντος και λοιπά κλινικοεργαστηριακά δεδομένα**

Βέλτιστη ενδοσκοπική παρακολούθηση και χειρισμός της δυσπλασίας

Journal of Crohn's and Colitis, 2023, **17**, 827–854
https://doi.org/10.1093/ecco-jcc/jjac187
Advance access publication 18 December 2022
ECCO Guideline/Consensus Paper

ECCO Guidelines on Inflammatory Bowel Disease and Malignancies

Hannah Gordon,[a,b] Livia Biancone,[c] Gionata Fiorino,[d,e] Konstantinos H. Katsanos,[f] Uri Kopylov,[g] Eman Al Sulais,[h] Jordan E. Axelrad,[i] Karthiha Balendran,[j] Johan Burisch,[k,l] Lissy de Ridder,[m] Lauranne Derikx,[n,o] Pierre Ellul,[p] Thomas Greuter,[q,r] Marietta Iacucci,[s,t] Caroline Di Jiang,[u] Christina Kapizioni,[v] Konstantinos Karmiris,[w] Julien Kirchgesner,[x] David Laharie,[y] Triana Lobatón [z,aa] Tamás Molnár,[bb] Nurulamin M. Noor,[cc] Rohit Rao,[dd] Simone Saibeni,[ee] Michael Scharl,[ff] Stephan R. Vavricka,[ff] Tim Raine[gg]



*In patients who have no colonic involvement, or disease limited to the rectum, no further IBD specific surveillance is indicated
**Including post liver transplant
***In patients who have not undergone surgery
****Dye-based chromoendoscopy (DCE), virtual electronic chromoendoscopy (VCE), high definition white light endoscopy (HD-WLE)

Visible vs invisible*	
Site	
Size	<2 cm favours endoscopic resection EMR or ESD can be considered for larger lesions
Shape	Polypoid (modified paris 1p or 1s) vs non polypoid (IIa, IIb, IIIc) borders (distinct vs indistinct)
Surface	Kudo or FACILE (frankfurt advanced chromoendoscopic IBD lesions)
Surroundings	Mucosal activity, other lesions in surrounding area, submucosal fibrosis
HGD	High-grade dysplasia
LGD	Low-grade dysplasia
Indefinite dysplasia	Unclassified atypia**

*When invisible dysplasia is detected from biopsies, the patient should be referred for a repeat colonoscopy with DCE or VCE with targeted and random biopsies, by an expert endoscopist, with the aim of unmasking dysplastic lesion

**Consider referral to expert GI histopathologist

Table 1. Therapeutic management of dysplasia in IBD

Endoscopic features	Therapeutic management	Follow-up
Polypoid lesion OR Non-polypoid lesion ≤2 cm without stigmata of invasive cancer or fibrosis and distinctive border	Endoscopic *en-bloc* resection [EMR, ESD, Hybrid ESD] Undertaken by expert endoscopist	Close surveillance with DCE or VCE + targeted biopsies HGD: 3 months for the first year then annually. Non-polypoid LGD: 6 months for the first year then annually. Polypoid <1 cm or pedunculated LGD: 12 months
Non-polypoid large lesion >2 cm without stigmata of invasive cancer or fibrosis and distinctive border	Endoscopic *en-bloc* resection [ESD] by expert endoscopist Surgery as an alternative to endoscopic resection	Intense surveillance with DCE or VCE + targeted and random biopsies Every 3 to 6 months for the first year and then annually
Unresectable large lesion [indistinctive borders], invasive cancer	Surgery	
Invisible dysplasia on random biopsies	Confirmation by second pathologist Repeat surveillance colonoscopy with DCE+random and targeted biopsies by an expert endoscopist	Unmasked visible dysplasia: as above Persistent unifocal invisible LGD: consider intensive DCE surveillance follow-up Persistent unifocal invisible HGD: consider colectomy
Indefinite dysplasia	Confirmation by second pathologist Optimise therapy and control inflammation Repeat surveillance colonoscopy with DCE or VCE +random and targeted biopsies in quiescent disease	Annual surveillance colonoscopy
Multifocal dysplasia LGD or HGD	Surgery In select cases of colonic lesions with discrete borders, *en-bloc* endoscopic resection can be considered following MDT discussion	Surgery should be performed in the majority of patients with multifocal LGD or HGD If endoscopic resection is undertaken, surveillance should be performed every 3 months for the first year then annually
Sporadic adenoma in IBD	Endoscopic *en-bloc* resection	Surveillance colonoscopy as per post-polypectomy guidelines

IBD, inflammatory bowel disease; LGD, low-grade dysplasia; HGD, high-grade dysplasia; DCE, dye-based chromoendoscopy; VEE, virtual electronic endoscopy; EMR, endoscopic mucosal resection; ESD, en-bloc resection; MDT, multidisciplinary team.