ΙΦΝΕ, Ήπαρ: Ανασκόπηση 2019

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Ιούνιος 2019

ΔΗΛΩΣΗ ΣΥΓΚΡΟΥΣΗΣ ΣΥΜΦΕΡΟΝΤΩΝ (Disclosures)

Abbvie, Janssen, Gilead, Merck, Pfizer, Takeda

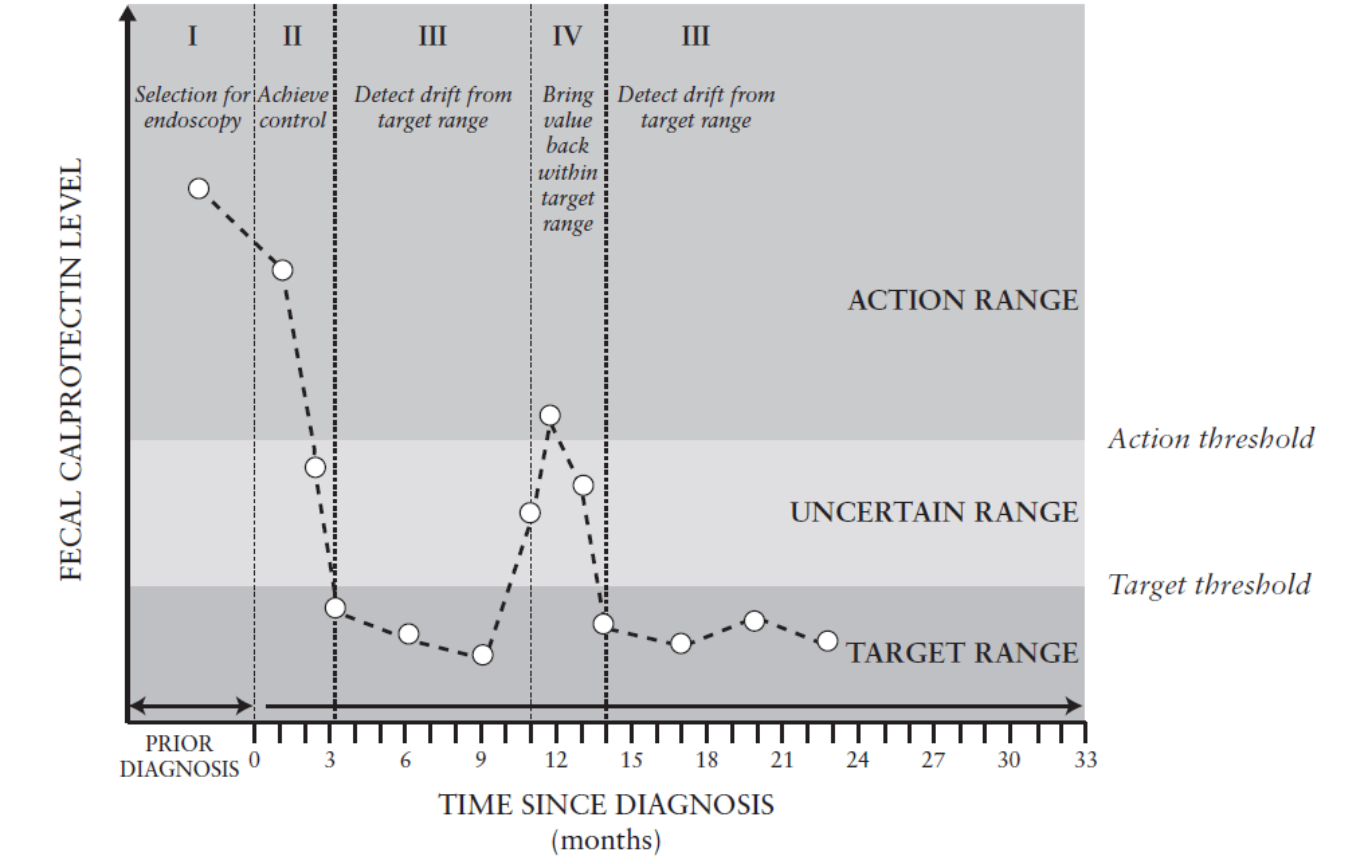
Υλικό Παρουσίασης

Guidelines

Landmark Studies

Practice Changing Research

ECCO-ESGAR Guideline for Diagnostic Assessment in IBD Part 1: Initial diagnosis, monitoring of known IBD, detections of complications



JCC, August 2018

ECCO-ESGAR Guideline for Diagnostic Assessment in IBD Part 2: IBD scores and general principles and technical aspects

- Scores

-clinical

-endoscopy

-MRI

-US

AGA, February 2019
Mild-to-Moderate Ulcerative Colitis

- *Standard dose, >2 grams mesalazine*
- *Rectal therapy for left sided or extensive colitis*
- *Proctitis, suppositories*
- *Suboptimal response:*

-high dose, >3 grams mesalazine

-rectal steroids

-budesonide mmx

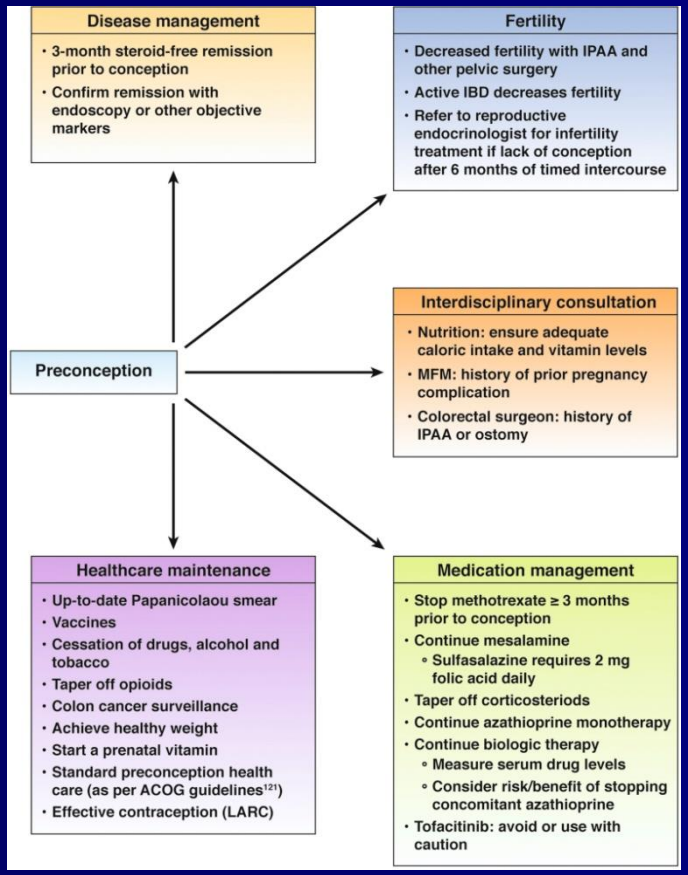
- *No probiotics*
- *No Curcumin*
- *No FMT (FDA Alert!)*

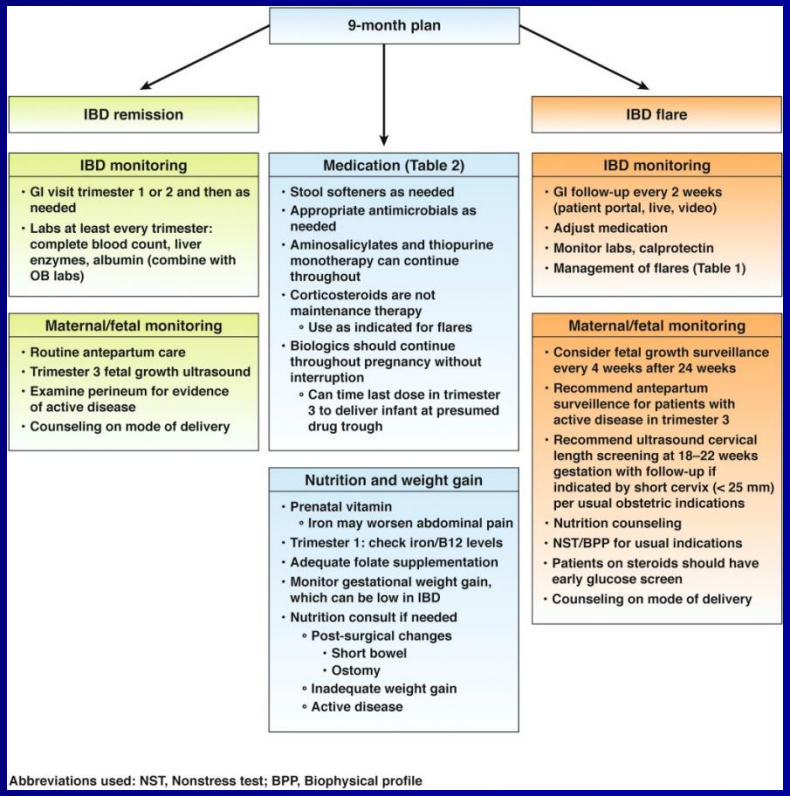
AGA Clinical Practice Update on functional gastrointestinal symptoms in patients with inflammatory bowel disease

- Rule out inflammation…
- Perform fecal calprotectin…
- Calpro indeterminate results, consider serial monitoring…
- If obstructive → anatomic abnormalities → imaging…
- Alternative pathophysiology: steatorrhea, bile acid diarrhea…
- Laxatives, Spasmolytics, Bile-acid sequestrants, hypomotility…
- FODMAPS diet…
- Psychological therapies…
- Exercise…
- CAM?

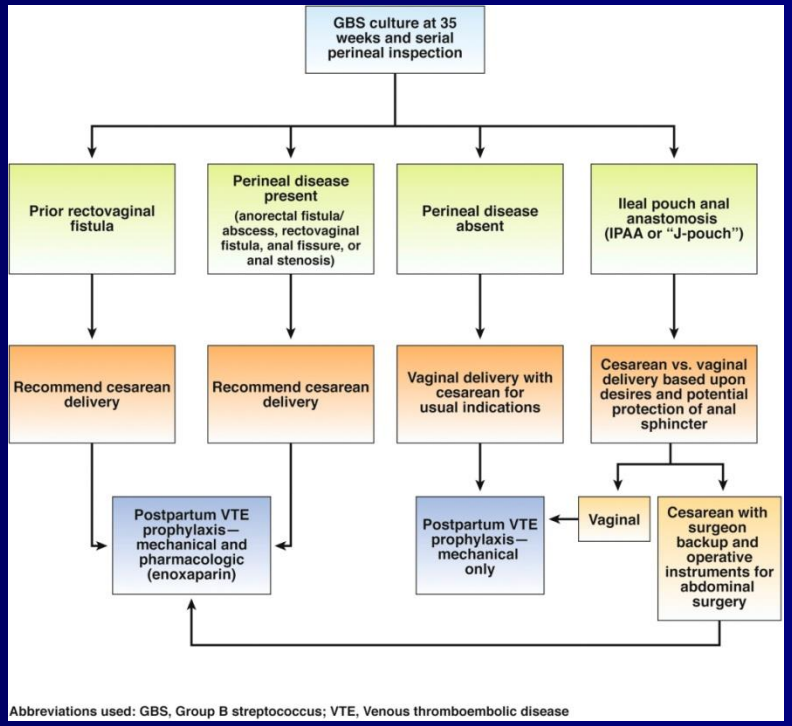
Colombel JF, CGH 2019

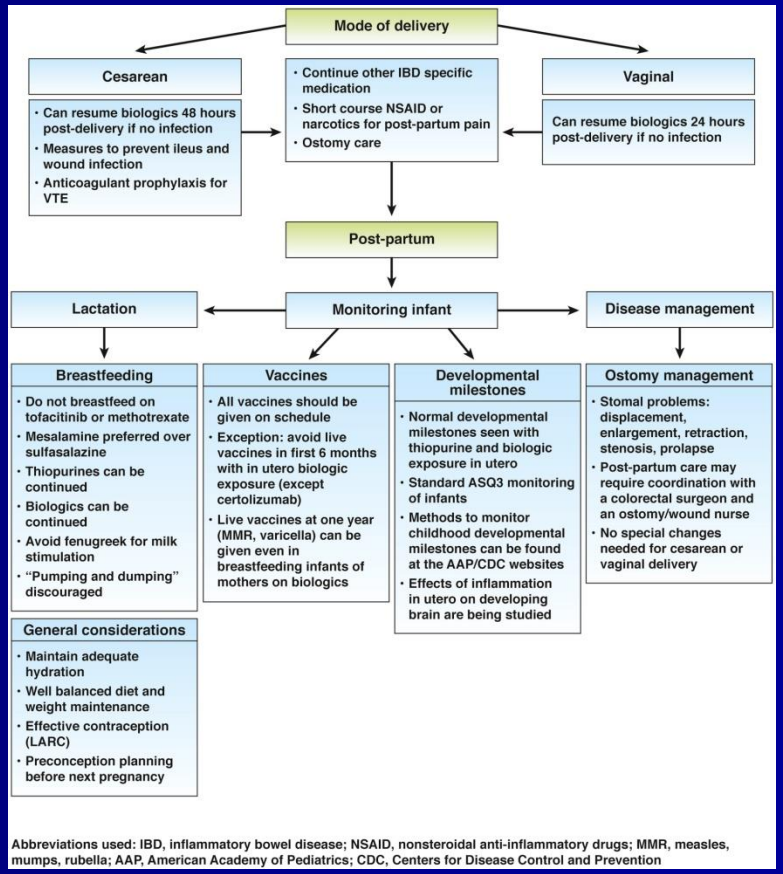
AGA, April 2019
Inflammatory Bowel Disease in Pregnancy Clinical Care Pathway





AGA, April 2019
Inflammatory Bowel Disease in Pregnancy Clinical Care Pathway





ΙΦΝΕ Φάρμακα και Κύηση

Table 2. Inflammatory Bowel Disease Maintenance Therapies During Pregnancy and Lactation

Medication	Maintenance dosing recommendation	Breastfeeding considerations
Aminosalicylates	Maintain prepregnancy dosing	
Mesalamine	All preparations are now phthalate-free	Compatible with breastfeeding No preparation preference Monitor infant for diarrhea
Sulfasalazine	Consider 2-mg folate supplement in pregnancy Azulfidine EN contains phthalate	Compatible with breastfeeding Mesalamine preferred
Immunomodulators	Dosing may be altered due to increased renal clearance with pregnancy. Therapeutic drug monitoring recommended	Routine infant monitoring not necessary
Cyclosporine (calcineurin inhibitor)	Limited data in pregnancy suggest associations with hypertension, gestational diabetes, preterm birth, low birthweight/SGA. Used as a salvage therapy.	Compatible with breastfeeding Minimal infant exposure, no reports of harm from breastfeeding
Methotrexate	Contraindicated in pregnancy. Stop 3 months before conception.	Limited human data. Not advised.
Thiopurines (azathioprine, 6-mercaptopurine)	Continue as monotherapy In appropriate patients, consider cessation of thiopurine as combination therapy, given possible association with increased infant infections. Use with caution in combination with allopurinol, which carries potential embryo toxic effects	Compatible with breastfeeding Minimal infant exposure, no reports of harm from breastfeeding
Small molecules		
Tofacitinib	Limited human data. Consider other options, particularly in first trimester	Limited human data. Not advised.
Biologics	Maintain prepregnancy dosing Continue dosing throughout all 3 trimesters If possible, plan final dose according to drug half-life to minimize transfer	Compatible with breastfeeding Encourage participation in pregnancy registries if not already done during pregnancy.
Adalimumab	Plan final pregnancy injection 2–3 wk before EDC and resume postpartum[a] (1–2 wk if weekly dosing)	
Certolizumab pegol	May continue scheduled dosing throughout pregnancy.	
Golimumab	Plan final pregnancy injection 4–6 wk before EDC and resume postpartum[a]	
Infliximab	Plan final pregnancy infusion 6–10 wk before EDC and resume postpartum[a] (If every-4-wk dosing, then 4–5 wk before EDC) Base dosing on prepregnancy weight during pregnancy and immediate postpartum	
Natalizumab	Plan final pregnancy infusion 4–6 wk before EDC and resume postpartum[a]	
Ustekinumab[b]/ Vedolizumab[b]	Plan final pregnancy dose 6–10 wk before EDC and resume postpartum[a] (If every-4-week dosing, then 4–5 wk before EDC)	
Corticosteroids	Reserved for active flares in pregnancy. Not recommended for planned maintenance therapy during pregnancy.	Compatible with breastfeeding Subtherapeutic infant exposure expected, even with flare dosing Avoiding feeding 1–2 h post-dose (non-enteric coated forms) can further minimize exposure but is not necessary
Antibiotics	Reserved for perianal disease and pouchitis and not recommended for planned maintenance therapy (amoxicillin/metronidazole preferred over ciprofloxacin)	Amoxicillin/clavulanic acid compatible with breastfeeding Ciprofloxacin preferred over metronidazole

EDC, estimated date of confinement; SGA, small for gestational age.
[a]48 hours post-delivery
[b]Limited pregnancy data

ACG Clinical Guideline, January 2019 Ulcerative Colitis in Adults

- **49 statements**

-diagnosis, assessment, prognosis

-goals for managing patients

-induction and maintenance of remission in mildly active UC

-induction and maintenance of remission in moderately active UC

-management of the hospitalized patient with acute severe UC

ACG Clinical Guideline, January 2019
Ulcerative Colitis in Adults

Table 3. Summary of key concept statements for the management of ulcerative colitis

Diagnosis, assessment, and prognosis of ulcerative colitis
1. The diagnosis of UC should be suspected in patients with hematochezia and urgency.
2. Infectious etiologies should be excluded at the time of diagnosis.
3. Colonoscopy with intubation of the ileum and biopsies of affected and unaffected areas should be obtained to confirm the diagnosis of UC by a trained pathologist with expertise in gastrointestinal pathology when possible.
4. Categories of disease extent include (i) proctitis (within 18 cm of the anal verge, distal to the rectosigmoid junction), (ii) left-sided colitis (extending from the sigmoid to the splenic flexure), and (iii) extensive colitis (beyond the splenic flexure).
5. If the terminal ileum is normal, further evaluation of the stomach and small bowel by upper endoscopy and cross-sectional imaging is not needed unless there are other symptoms or findings to suggest proximal gastrointestinal involvement or a diagnosis of CD rather than UC.
6. Definitions of disease severity are needed to guide treatment decisions; definitions should be based on (i) PROs (bleeding and normalization of bowel habits), (ii) inflammatory burden (endoscopic assessment including extent and severity and markers of inflammation), (iii) disease course (need for hospitalization, need for steroids, and failure to respond to medications), and (iv) disease impact (functionality and QoL).
7. FC can be used in patients with UC as a noninvasive marker of disease activity and to assess response to therapy and relapse.
Goals for managing patients with ulcerative colitis
8. UC is a chronic condition for which therapy is required to induce and maintain remission; therapeutic decisions should be categorized into those for (i) induction and (ii) maintenance, with a goal of obtaining and maintaining a steroid-free remission.
9. Strategies for management of UC should reflect the patient's and provider's goals and recognize the chronic nature of the disease.
10. Corticosteroid-free remission may be defined based on symptoms, endoscopic findings, or disease impact without ongoing corticosteroid use. Symptomatic remission relates to improvement in PROs, whereas endoscopic healing is defined as restoration of intact mucosa without friability. Deep remission is a combination of symptomatic remission and endoscopic healing and is a preferred goal of management.
11. Selection of induction and maintenance therapies for UC should be based on disease extent, severity, and prognosis.
12. Initial treatment of UC should focus on restoration of normal bowel frequency and control of the primary symptoms of bleeding and urgency. An endoscopically healed mucosa is associated with sustained remission and reduced risk of colectomy.
13. Histological healing is associated with some improved clinical outcomes but has not yet been validated prospectively as an end point of treatment.
14. Control of mucosal inflammation may reduce dysplasia risk.
15. Given the chronic nature of UC and the therapies for UC, monitoring for disease-related and drug-related complications is important. This should incorporate preventive strategies as outlined in a separate guideline from the ACG.
16. Routine visits to assess the state of UC are recommended to monitor for relapse and address health maintenance needs.
17. Patients with UC should be screened for coexistent anxiety and depressive disorders, and when identified, patients should be provided with resources to address these conditions.
Induction of remission in mildly active ulcerative colitis
18. Patients with mildly active UC and a number of prognostic factors associated with an increased risk of hospitalization or surgery should be treated with therapies for moderately to severely active disease (Table 8). Each prognostic factor carries a different weight and must be discussed in a shared decision-making fashion with the patient. For example, age alone is a weaker prognostic factor than severe endoscopic activity. However, young age combined with another factor may represent sufficient criteria to treat according to the moderately to severely active disease protocol.
19. Patients with mildly active UC should be reassessed to determine response to induction therapy within 6 weeks.
20. FMT requires more study and clarification of treatment before use as a therapy for UC.
21. Complementary therapies such as probiotics and curcumin require further study with adequate power and clarification of end points.
Induction of remission in moderately to severely active ulcerative colitis
22. Strategies for the management of the nonhospitalized patient with moderately to severely active UC are similar with the exception of a few considerations in which the data exist specifically for a patient with moderately active UC:
a. 5-ASA therapy could be used as monotherapy for induction of moderately but not severely active UC.
b. In patients with moderately active UC, consider nonsystemic corticosteroids such as budesonide MMX before the use of systemic therapy.
c. In patients with severely active UC, consider systemic corticosteroids rather than topical corticosteroids.
23. Robust data on combination anti-TNF and immunomodulator therapy in moderately to severely active UC exist only for infliximab and thiopurines.
24. Patients who are primary nonresponders to an anti-TNF (defined as lack of therapeutic benefit after induction despite adequate drug levels) should be evaluated and considered for alternative mechanisms of disease control (e.g., in a different class of therapy) rather than cycling to another drug within the anti-TNF class.

Table 3. (*continued*)

25. In patients with moderately to severely active UC who had an initial response but subsequently lost efficacy to one anti-TNF therapy, we recommend alternative anti-TNF therapy (but not the biosimilar to the original brand) compared with no treatment for induction of remission.
26. The patient with nonresponse or loss of response to therapy should be assessed with therapeutic drug monitoring to identify the reason for lack of response and whether to optimize the existing therapy or to select an alternate therapy.
27. Obtain consultation with a surgeon and consider colectomy in patients with moderately to severely active UC who are refractory or intolerant to medical therapy.
Maintenance of remission in patients with previously moderately to severely active ulcerative colitis
28. 5-ASA therapy for maintenance of remission is likely not as effective in previously severely active UC compared with previously moderately active UC.
29. Budesonide MMX has not been studied for maintenance of remission of previously moderately to severely active UC.
30. Most clinical trials and available data demonstrate a benefit of using the steroid-sparing therapy that induces remission to maintain that remission.
31. There is insufficient evidence supporting a benefit for proactive therapeutic drug monitoring in all unselected patients with UC in remission.
32. We suggest elective proctocolectomy in patients with UC failing maximal medical management.
Management of the hospitalized patient with acute severe ulcerative colitis
33. All patients admitted with ASUC should have stool testing to rule out CDI.
34. All patients with ASUC should undergo a flexible sigmoidoscopy within 72 hr, and preferably within 24 hr of admission. This should be used to assess endoscopic severity of inflammation and to obtain biopsies to evaluate for CMV colitis.
35. All patients with ASUC should be assessed for the presence of toxic megacolon on a regular basis during the hospital admission.
36. Response in patients with ASUC should be monitored using stool frequency, rectal bleeding, physical examination, vital signs, and serial CRP measurements.
37. NSAIDs, opioids, and medications with anticholinergic side effects should be avoided in ASUC.
38. In patients failing to adequately respond to medical therapy by 3–5 days or with suspected toxicity, surgical consultation should be obtained.
39. The choice between infliximab and cyclosporine should be based on provider experience with the agent, history of previous failure of immunomodulator or anti-TNF therapy, and serum albumin.
40. Toxic megacolon, colonic perforation, severe refractory hemorrhage, and refractoriness to medical therapy are indications for surgery in patients with ASUC.
41. Infliximab and cyclosporine do not increase postoperative complications of colectomy, and surgery should not be deferred based on this exposure.
Colorectal cancer prevention in ulcerative colitis
42. Screening and subsequent surveillance colonoscopy to assess for dysplasia in individuals with UC of extent greater than the rectum should start 8 years after diagnosis.
43. Patients with UC and PSC should undergo a screening colonoscopy at the time of diagnosis of UC and surveillance annually thereafter.
44. Surveillance colonoscopies in patients with UC should be performed at 1- to 3-year intervals based on the combined risk factors for CRC in UC and the findings on previous colonoscopy. Specific interval should be based on combined risk factors and findings from previous examinations.
45. During colonoscopic examination in patients with UC, the endoscopist should identify raised lesions and abnormal pit patterns and perform targeted biopsies. Endoscopically discrete lesions should be removed, clearly labeling and separating distinct lesions and segments of the colorectum.
46. Most neoplasia in UC is visible with standard- or high-definition white-light examinations.
47. It is unclear whether segmental random biopsies are still required during surveillance colonoscopy in UC.
48. Pathologic interpretation of UC-associated neoplasia should be performed by a pathologist experienced in gastrointestinal pathology, and neoplastic findings should be reviewed by a second experienced pathologist.
49. When dysplasia in UC of any grade is discrete and has been completely removed, proctocolectomy may not be necessary. If surgery is not performed, subsequent surveillance colonoscopy should initially be performed at shortened intervals.
50. When dysplasia in UC is not resectable or is multifocal, the patient should be referred for proctocolectomy.
51. Patients with UC who have extensive inflammatory polyps may not be able to have adequate surveillance and should be informed about this fact and that more frequent surveillance or surgery may be required.
52. No medical therapy has demonstrated sufficient prevention of dysplasia or CRC to avoid colonoscopic surveillance in UC.
53. Patients with UC-associated dysplasia who are undergoing ongoing active surveillance may benefit from the use of augmented visualization by dye spray chromoendoscopy in their first examination after UC-associated dysplasia was detected.
54. Fecal DNA testing and CT colonography are not recommended for screening or surveillance of UC-associated neoplasia because of insufficient evidence.

5-aminosalicylate, 5-ASA; ACG, American College of Gastroenterology; ASUC, acute severe ulcerative colitis; CD, Crohn's disease; CDI, *Clostridioides difficile* infection; CMV, cytomegalovirus; CRC, colorectal cancer; CRP, C-reactive protein; CT, computed tomography; DVT, deep venous thrombosis; FC, fecal calprotectin; FMT, fecal microbiota transplantation; MMX, multi-matrix; NSAID, nonsteroidal anti-inflammatory drug; PRO, patient-reported outcome; PSC, primary sclerosing cholangitis; QoL, quality of life; TNF, tumor necrosis factor; UC, Ulcerative colitis.

Ελκώδης Κολίτιδα
Δείκτες Δραστηριότητας

New ACG UC Activity Index

	Remission	Mild	Moderate-Severe	Fulminant
Stools (#/day)	Formed stools	<4	>6	>10
Blood in stools	None	Intermittent	Frequent	Continuous
Urgency	None	Mild, occasional	Often	Continuous
Hemoglobin	Normal	Normal	<75% of normal	Transfusion required
ESR	<30	<30	>30	>30
CRP (mg/L)	Normal	Elevated	Elevated	Elevated
Fecal calprotectin (µg/g)	<150-200	>150-200	>150-200	>150-200
Endoscopy (Mayo subscore)	0-1	1	2-3	3
UCEIS	0-1	2-4	5-8	7-8

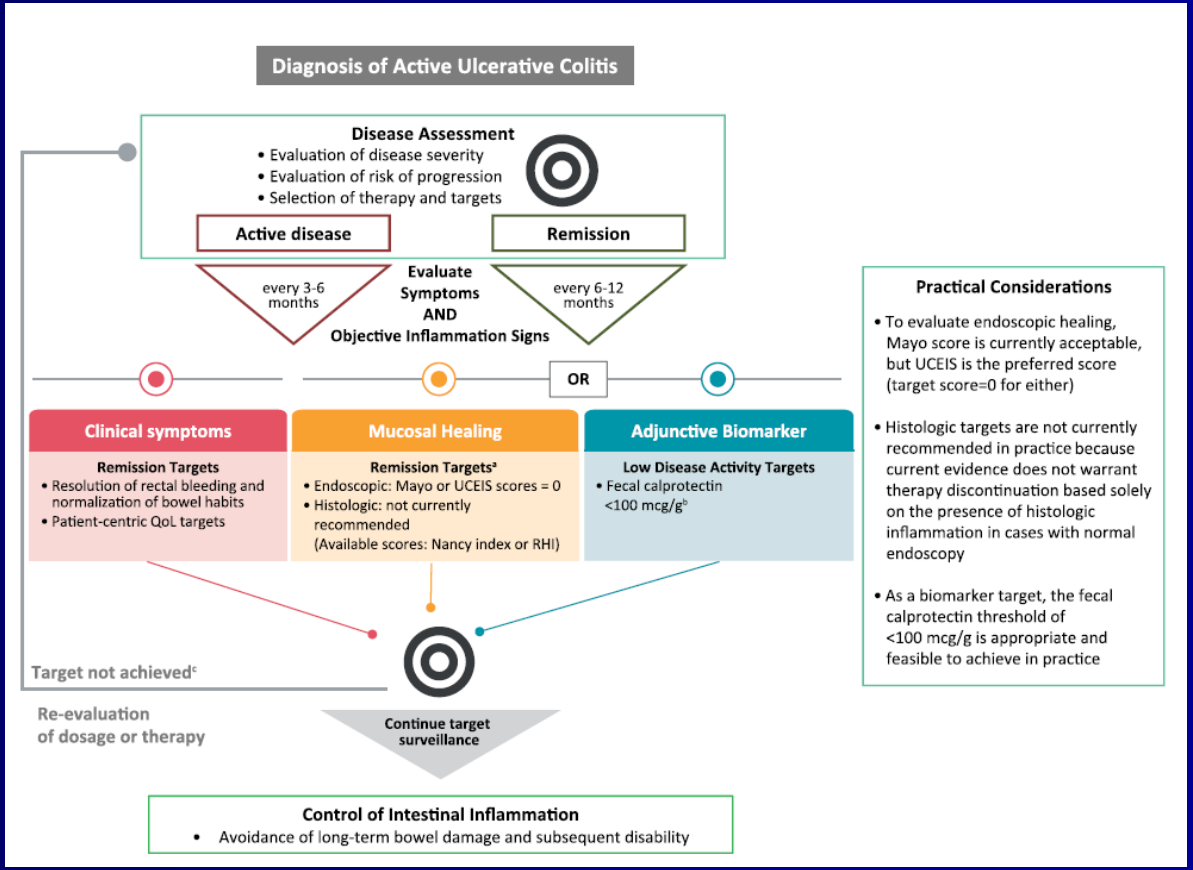
Rubin DT, et al. *Am J Gastroenterol.* 2019;114(3):384-413.

A Treat To Target Update in UC
A Systematic Review

	STRIDE Consensus Targets	Accumulating Evidence	Optimized Targets
Clinical Targets and PROs	Resolution of rectal bleeding and normalization of bowel habits should be the target. Monitor every 3 months until symptom resolution and every 6 months thereafter.	Discrepancy between symptom normalization and endoscopic activity.	Validated PRO scores and tools/technologies for PRO reporting.
Endoscopic Targets	Absence of ulceration is the target (minimum score of 1). Assessments should be done every 3-6 months after start of therapy.	Utility of UCEIS and modified Mayo scores. More stringent endoscopic resolution associated with better outcomes (Mayo score = 0).	Validated UCEIS and Mayo scores. Mayo score = 0
Histological Targets	Not recommended as a target because of insufficient evidence.	Histological healing associated with endoscopic healing and can predict long-term outcomes.	Validated histological index. Nancy and Robarts scores as promising potential tools in clinical practice and clinical trials
Adjunctive Biomarker Targets	CRP and fecal calprotectin are adjunctive measures of inflammation but NOT treatment targets. Failure of CRP or fecal calprotectin normalization should prompt endoscopic evaluation.	Fecal calprotectin responsive to treatment induction and dose response.	Validated fecal calprotectin cut-off value with demonstrated specificity, sensitivity, and reliability. Home-based test development.
Novel Future Targets	Molecular evidence of inflammation (intestinal permeability) may be helpful with assessing disease activity in patients who demonstrate endoscopic healing but still experience symptoms. Methods for detecting molecular inflammation will require extensive research to demonstrate its association with disease short-term and long-term outcomes.		

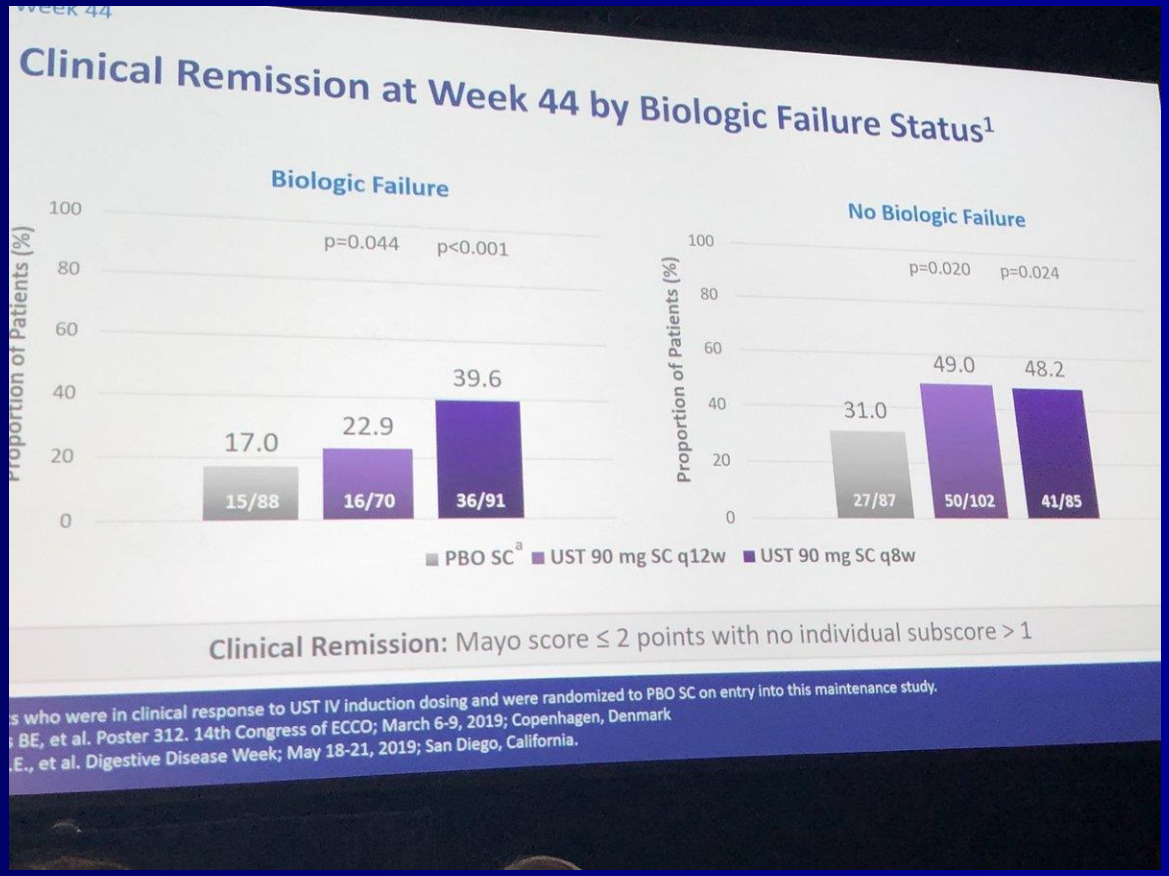
Ungaro, Am J Gastroenterol 2019

A Treat To Target Update in UC
A Systematic Review



Ungaro, Am J Gastroenterol 2019

Μελέτη UNIFI:
Ustekinumab και Ελκώδης Κολίτιδα



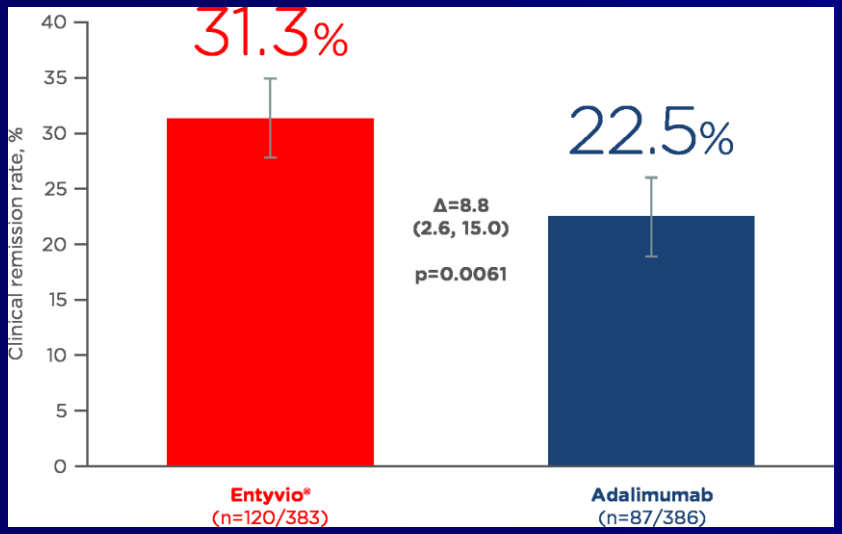
Tofacitinib: EMA Puts Temporary Restrictions on Tofacitinib Due to PE Risk

- These include patients with heart failure, cancer, inherited coagulation disorders, a history of venous thromboembolism, either deep venous thrombosis (DVT) or PE, as well as patients taking combined hormonal contraceptives or hormone replacement therapy or who are scheduled to have major surgery.
- Prescribers should also consider other factors that may increase the risk for PE, including age, obesity, smoking, or immobilization, the EMA said in a news release.
- The recommendation stems from results of an ongoing postmarketing study that is evaluating the safety of tofacitinib 5 mg twice daily and tofacitinib 10 mg twice daily in comparison with a tumor necrosis factor (TNF) inhibitor in patients with rheumatoid arthritis (RA) aged 50 years or older who have one or more cardiovascular risk factors.
- Preliminary results found 19 cases of PE in 3883 patient-years in the tofacitinib 10-mg twice-daily arm, compared with three cases in 3982 patient-years in the TNF-inhibitor arm. Additionally, there were 45 deaths from all causes in 3897 patient-years in the 10-mg twice-daily arm, compared with 25 deaths in 3982 patient-years in the TNF-inhibitor group.
- The EMA notes that because the 10-mg twice-daily dose is the only recommended starting dose for the treatment of ulcerative colitis, "patients with this condition who are at high risk of blood clots must not be started on Xeljanz. Patients at high risk currently taking this dose for any condition must be switched to alternative treatments."

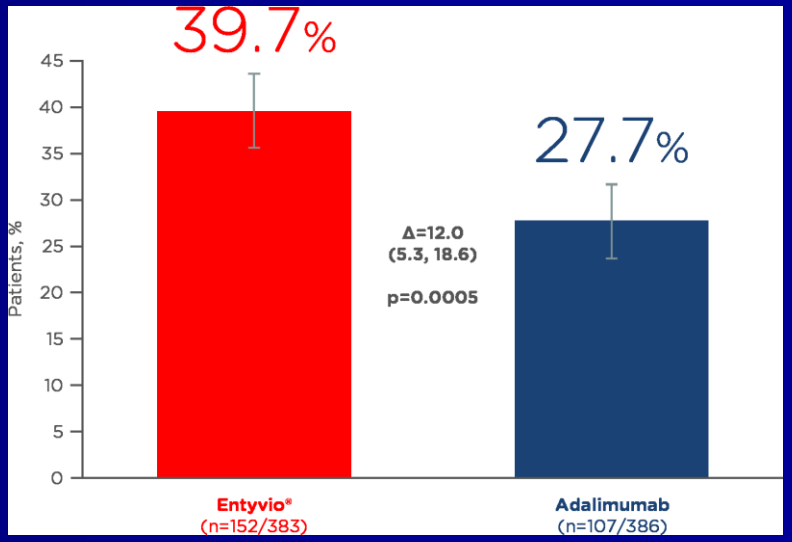
May 17, 2019

VARSITY
Vedolizumab vs Adalimumab in UC
(First Head to head study In IBD!)

Clinical Remission



Mucosal healing



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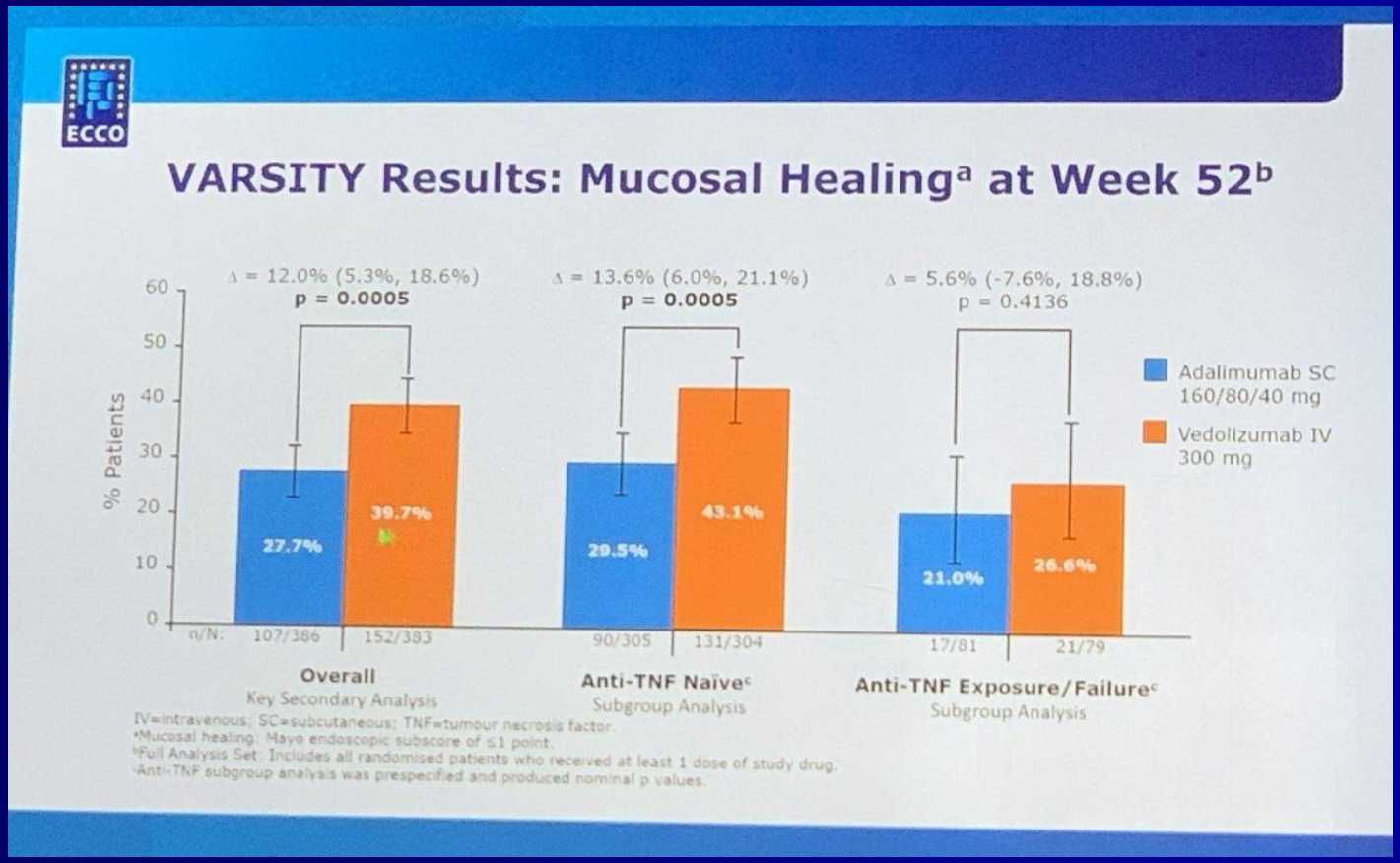


Effects of Subcutaneous Vedolizumab on Health-Related Quality of Life and Work Productivity in Patients with Ulcerative Colitis: Results from the Phase 3 Visible 1 Trial

- Vedolizumab iv 300 W2, W6
- Clinical Response W6: n=216
- sc 108/2weeks vs iv 300/8weeks or placebo
- W 52 results
- IBDQ: 180.7/170.7/135.2
- EQ5 VAS: 76.1/ 71.4/ 58.1
- WPAI-UC: better than placebo
- Further studies, validation

Sa1878, Vermeire, DDW 2019

Biosimilar to Infliximab Is Effective for Inducing Remission in Crohn Disease

- Randomised, double blind, Phase 3, non inferiority
- 1:1:1:1, switch Week 30

-CT-P13 → CT-P13

-CT-P13 → IFX

-IFX → IFX

-IFX → CT-P13

- 220 pts
- W6, W14, W30 CDAI-70 response
- W54 treatment emergent adverse events
- Non inferiority established

Duc Ye, Lancet 2019

Early Combined Immunosuppression may be Effective and Safe in Older Patients With Crohn's Disease

-1981 patients, 311 were ≥60 years (15.7%)
-early combined immunosuppression (ECI) 173
-conventional management (CM) 138
-Crohn's disease-related complications, 14 patients died (24 months)
-6.4% vs 14.5% (3.5% vs 5.8%).
-Corticosteroid-free clinical remission
-(<60 years, ECI (72.6%) vs CM (64.4%): relative risk [RR], 1.06
-vs ≥60 years, ECI (74.8%) vs CM (63.0%): RR, 1.09
-Time to major adverse outcome
-(<60 years: hazard ratio [HR], 0.71 [0.53-0.96] vs ≥60 years: HR, 0.69 [0.31-1.51] ECI vs CM

Singh, APT 2019, Post Hoc Analysis of REACT

Artificial Intelligence accurately grades IBD disease severity

- Ulcerative Colitis
- Michigan University, Endoscopic Imaging Database, EMHR
- 2778 pts, 14,682 images, deep learning CNN.
- Mayo Score
- 2 human reviewers vs CNN: no difference (in still images)
- 50 UC videos with good bowel prep?

Stidham, Abstract 336, DDW 2019

Fibrosis and IBD

- *…An expert consensus to standardise definitions, diagnosis and treatment targets for anti-fibrotic stricture therapies in Crohn's disease…*
- *…Anti-fibrotic Drugs for Crohn's Disease: Ready for Prime Time?...*
- *…Treatments for Crohn's Disease-Associated Bowel Damage: A Systematic Review…*
- *…Noninvasive Multimodal Methods to Differentiate Inflamed vs Fibrotic Strictures in Patients With Crohn's Disease…*
- *…How I Approach the Management of Stricturing Crohn's Disease…*

EASL Clinical practice Guideline 2019: Drug Induced liver Injury

-Risk Factors
(Age, Sex, Race, Ethnicity, Drugs, Metabolic Syndrome, Genetics)
-Immune-Mediated Hepatitis
-Hy's Law

Table 10. Practical approaches towards managing suspicion of DILI.

Medical history	Search for recent therapies even if they have finished (*i.e.* antibiotics). Do not forget to ask about herbs and dietary supplements.
Case characterisation	Classify liver injury based on R ([ALT/ULN]/[ALP/ULN]) using the first blood test available after DILI detection.
Case investigation	If hepatocellular pattern: test for RNA-HCV and IgM anti-HEV in addition to HAV, HBV and autoimmune serology. If cholestatic/mixed damage with jaundice: perform cholangiography in addition to ultrasound.
Case adjudication	Use the CIOMS scale as a guide for complete data requirement, but do not exclusively rely on it for causality assessment.
Liver biopsy	It is not required for diagnosis. Not necessary if the suspected drug is a known hepatotoxic compound and the outcome is favourable.
Follow-up	Careful scrutiny of hepatocellular cases with jaundice in females and all other cases with altered INR for impending liver failure. In the long-term pay attention to abnormal ALP and bilirubin after 30 days for the risk of chronicity.
Therapy	Stop all non-essential drugs. Steroids can be tried if AIH is an option and in cases with marked hypersensitivity features.

EASL Clinical practice Guideline 2019: Drug Induced liver Injury

Table 3. Definitions, phenotypes and drugs associated with hepatic adverse reactions.

Phenotypes of DILI	Case definition[160]	Medications associated with the phenotype
Idiosyncratic DILI	An adverse hepatic reaction that is unexpected on the basis of the pharmacological action of the drug administered. Three patterns of DILI determined using earliest identified elevation of liver enzymes levels. Initially ALT activity (patients ALT/upper limit of normal (ULN) of ALT) and ALP activity (patients ALP/ULN of ALP) is calculated. Then ALT/ALP ratio (R) is determined. Hepatocellular pattern: If ALT alone is elevated ≥5-fold above ULN or R ≥5. Cholestatic pattern: ALP alone is elevated ≥2-fold above ULN or R ≤2. Mixed pattern: R >2 to <5. Chronic DILI: DILI with acute presentation where there is evidence of persistent liver injury at >1 year after its onset.	Antimicrobials: Amoxicillin-clavulanate, erythromycin, flucloxacillin, interferon alpha/peginterferon, isoniazid, ketoconazole, minocycline, nevirapine, nitrofurantoin, pyrazinamide, rifampicin, co-trimoxazole, and sulfonamides. Central nervous system: Carbamazepine, chlorpromazine, dantrolene, halothane, phenytoin and valproate. Cardiovascular: Amiodarone, hydralazine, methyldopa, quinidine, statins (atorvastatin and simvastatin). Immunomodulatory: Azathioprine/6-mercaptopurine, infliximab, interferon beta, methotrexate and thioguanine. Antineoplastic: Busulfan, floxuridine and flutamide. Rheumatologic: Allopurinol, auronofin/Gold products, diclofenac, ibuprofen, nimesulide and sulindac. Endocrine: Anabolic androgenic steroids, estrogens/progestins and propylthiouracil. Others: Disulfiram and ticlopidine.
Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS syndrome)	Drug-induced hypersensitivity involving multiple organs with systemic manifestations.	Anticonvulsants (carbamazepine, phenytoin and phenobarbitone), minocycline, allopurinol, abacavir and nevirapine.
Drug-induced autoimmune hepatitis	Patient presenting with acute DILI with serological and/or histological markers of idiopathic autoimmune hepatitis.	Diclofenac, halothane, indomethacin, infliximab, methyldopa, minocycline, nitrofurantoin and statins.
Secondary sclerosing cholangitis	Patients presenting with acute DILI with histological and/or magnetic resonance cholangiopancreatography evidences similar to those of primary sclerosing cholangitis.	Amiodarone, atorvastatin, amoxicillin-clavulanate, gabapentin, infliximab, 6-mercaptopurine, sevoflurane and venlafaxine.
Granulomatous hepatitis	Presence on liver biopsy of granulomas (focal accumulation of modified macrophages) that are attributed to exposure to one or more medication.	Allopurinol, carbamazepine, methyldopa, phenytoin, quinidine and sulphonamides.
Acute fatty liver	Clinical syndrome of rapid development of liver and other organ failure associated with extensive microvesicular steatosis.	Amiodarone, didanosine, stavudine, valproate and zalcitabine.
Drug-associated fatty liver disease	Non-alcoholic fatty liver disease attributable to exposure specific medications.	Methotrexate, 5-fluorouracil, irinotecan, tamoxifen, corticosteroids, lomitapide and mipomerson.
Nodular regenerative hyperplasia	Diffuse nodularity within the liver with characteristic arrangements of hepatocytes at the centre and periphery of nodule.	Azathioprine, busulphan, bleomycin, cyclophosphamide, chlorambucil, cysteine arabinoside, carmustine, doxorubicin, 6-thioguanine and oxaliplatin.
Ductopenic (vanishing bile duct) syndrome	Chronic cholestasis associated with bile duct loss.	Azathioprine, androgens, amoxicillin-clavulanate, carbamazepine, chlorpromazine, erythromycin, estradiol, flucloxacillin, phenytoin, terbinafine and co-trimoxazole.
Liver tumours	Characteristics of hepatocellular adenoma or carcinoma based on established histological, computed tomography or magnetic resonance imaging features.	Anabolic androgenic steroids and oral contraceptives.

ALP, alkaline phosphatase; ALT, alanine aminotransferase; DILI, drug-induced liver injury; ULN, upper limit of normal.

Decision to stop drug administration

The final decision to discontinue study medication is up to the judgement of the clinician responsible for the patient. Thresholds for treatment discontinuation in clinical trials (not post-marketing) suggested by the FDA guidance[345] are:

- ALT or AST >8 × ULN
- ALT or AST >5 × ULN for more than 2 weeks
- ALT or AST >3 × ULN and (TBL >2 × ULN or INR >1.5)
- ALT or AST >3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)

Primary Biliary Cholangitis
2018 Practice Guidance AASLD

Diagnosis

- two of these three criteria need to be met:
- 1) cholestatic pattern of liver enzyme elevation (mainly alkaline phosphatase);
- 2) presence of antimitochondrial antibody (AMA) or other PBC-specific autoantibodies, including sp100 or gp210, and;
- 3) histologic findings consistent with PBC.
- AMA-negative PBC can be diagnosed without a liver biopsy if other criteria are met, including cholestatic liver tests and PBC-specific autoantibodies such as sp100 or gp210.
- Perform liver biopsy for suspected concomitant autoimmune hepatitis (AIH) when alanine aminotransferase activity is more than five times the upper limit of normal.

Treatment

- Prescribe ursodeoxycholic acid (UDCA; 13 to 15 mg/kg/day) for patients who have abnormal liver enzyme levels, regardless of histologic stage of PBC.
- Evaluate biochemical response to UDCA at 12 months after treatment; in patients with inadequate response, consider treatment with OCA, starting at 5 mg/day.
- Consider fibrates as off-label alternatives for patients with inadequate response to UDCA.
- Use OCA and fibrates with caution in patients with decompensated liver disease.

Bezafibrate in primary biliary cholangitis

- Double blind, Placebo-controlled, phase III, 24 months
- 100 patients, inadequate response to UDCA
- 400 mg bezafibrate
- Primary Outcome: Complete Biochemical Response

-31% vs 0%

- Normal ALP:

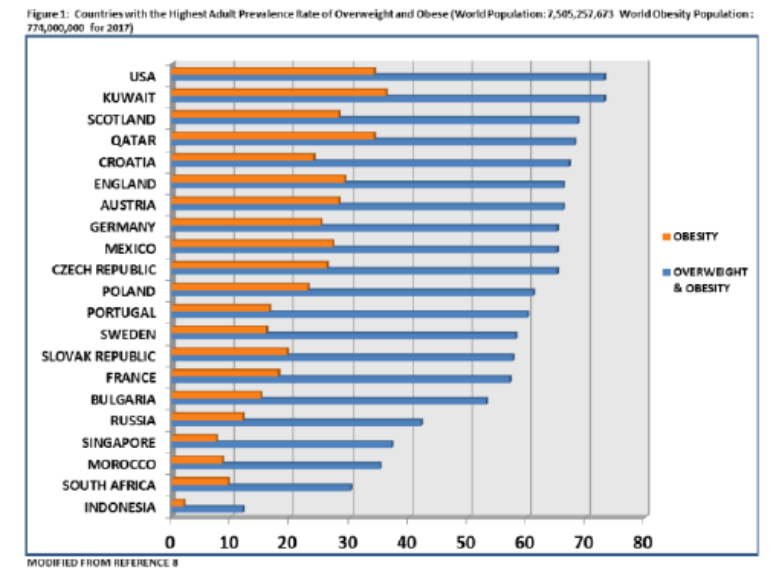
-67% vs 2%

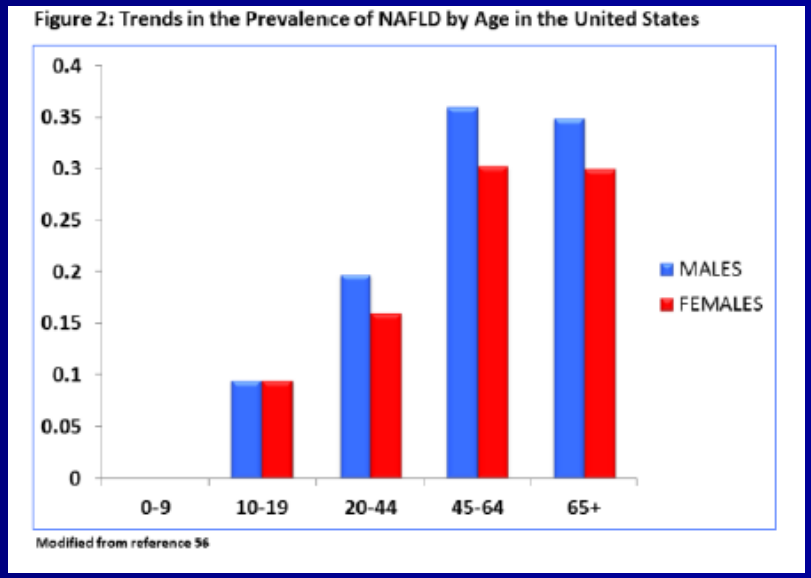
- Add on obeticholic acid triple therapy safe and effective

Corpechot, NEJM 2018
Smets, ILC 2019

The NAFLD epidemic…

1 in 5 young adults has steatosis, 1 in 40 has fibrosis

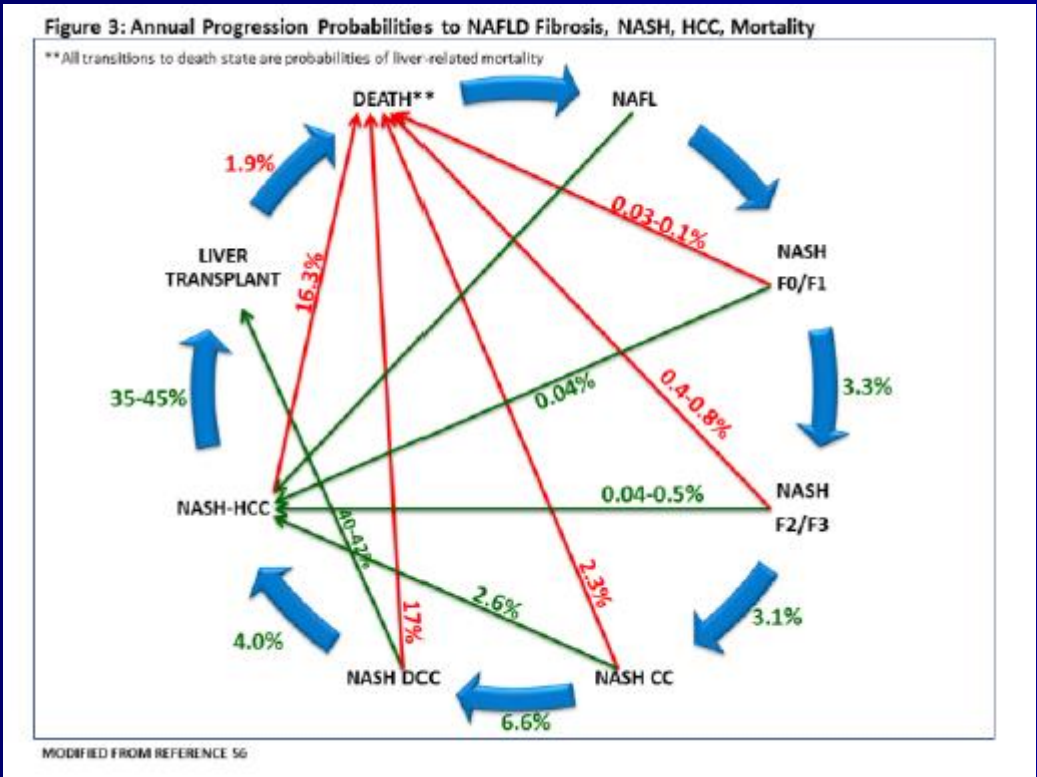




International NASH Day, June 12th

Younossi, J Hepatol 2019

NAFLD liver risks



Younossi, J Hepatol 2019

OBETICHOLIC ACID IMPROVES LIVER FIBROSIS AND OTHER HISTOLOGICAL FEATURES OF NONALCOHOLIC STEATOHEPATITIS (NASH)

- Phase 3 REGENERATE study, interim analysis, month 18
- 931 biopsy confirmed NASH, F2-F3
- OCA 10, OCA 25, placebo
- OCA 25 mg dose:

-improved fibrosis in ¼ of patients (23.1%)

-65,6% normalized ALT

-Pruritus 51% vs 19%

-9% discontinued

Younossi, ILC 2019

Beta-Blocker Therapy Might Prevent Cirrhosis Progression

- Spain, RCT, 201 patients with compensated cirrhosis and clinically significant portal hypertension (CSPH, >10 mm Hg)
- Beta blocker responsive (iv propranolol 10% drop HVPG)
- Propranolol vs placebo, carvedilol vs placebo
- 37 months f-up
- Decompensation or death 16% vs 27%
- Lower incidence of ascites

Villanueva, Lancet 2019

Long Term Albumin Administration in decompensated cirrhosis (ANSWER)

- 431 patients were included in the modified ITT analysis.
- 38 of 218 patients died in the SMT plus HA group
- 46 of 213 in the SMT group.
- Overall 18-month survival significantly higher in the SMT plus HA than in the SMT group

  (Kaplan-Meier estimates 77% *vs* 66%; p=0·028)
- 38% reduction in the mortality hazard ratio

  (0·62 [95% CI 0·40–0·95]).
- 46 (22%) patients in the SMT group and 49 (22%) in the SMT plus HA group had grade 3–4 non-liver related adverse events.
- 1 month on treatment serum albumin > 4,1: 93% survival

Caraceni, PS 83, ILC 2019

Best Practice Advice on Coagulation in Patients with Cirrhosis

- Clinicians should not routinely correct thrombocytopenia and coagulopathy for low-risk procedures such as band ligation of varices, paracentesis, and thoracentesis.
- For active bleeding and to minimize bleeding in high-risk procedures:
- A platelet count target >50,000 is still advised.
- Less reliance on international normalized ratio (INR) as a measure of hemostasis is advised.
- New measures of hemostasis including fibrinogen level (target >120 mg/dL) and viscoelastic tests that are global tests of clot formation, such as thromboelastography (TEG), are becoming a part of routine practice.
- The use of procoagulants, typically platelets and fresh frozen plasma, can lead to infectious, transfusion-related, and immunologic complications if overutilized. Alternatives to consider include:
- Antifibrinolytic therapy, such as tranexamic acid, in patients with persistent bleeding from mucosal oozing or puncture wound
- Desmopressin, in patients with renal failure
- Anticoagulation considerations:
- In patients with symptomatic deep venous thrombosis (DVT) or portal vein thrombosis (PVT), systemic heparin infusion is recommended.
- Treatment of incidental PVT should be considered in transplantation candidates, as extensive thrombosis could impact surgical candidacy.
- For PVT therapy, low-molecular-weight heparin, direct-acting anticoagulants, and vitamin K antagonists are recommended.
- Once anticoagulation for PVT is started, 6-month follow-up imaging is recommended to assess efficacy.

O' Leary, Gastroenterology 2019

Long-Term Clinical Outcomes After Eradication of HCV Infection with Direct-Acting Antiviral Therapy

- 9900 HCV pts, 23 hepatology clinics, France
- 7334 DAAs
- Median follow up 33 months
- 218 died, 258 HCC, 106 decompensated
- DAAs:

-lower risk of HCC (HR 0.66 95% CI 0.46-0.93)

-all cause mortality (HR 0.48 95% CI 0.33-0.70)

Carrat, Lancet 2019

A 6-Week Direct-Acting Antiviral Regimen for Chronic HCV Infection

- three-drug regimen JNJ-4178:

1. AL-335 (NS5B polymerase inhibitor) 800 mg daily,
2. odalasvir (NS5A inhibitor) 25 mg daily,
3. simeprevir (protease inhibitor) 75 mg daily

- Phase IIb, 6 vs 8 weeks
- 180 patients per arm
- SVR 12
- 98.9% vs 97.8%

Zeuzem, Hepatology 2019

Comparison of tenofovir and entecavir on the risk of hepatocellular carcinoma and liver related events in patients with chronic hepatitis B

Korean Nationwide Cohort Study

- 24,156 patients
- TDF: 12,692, ETV: 11,464
- Annual risk of HCC: 0.89 vs 1.19 per 100 patient/years

Multi center (4), Korean

- 2,897 patients
- Annual risk of HCC: 1.69 vs 1.92
- No statistical difference in HCC or death/OLT

Hong Kong, Territorywide Cohort study

- 1309 TDF/28,041 ETV: PS matched 5years HCC1.2% vs 2.3%

Is One NUC better than the other?

Choi, JAMA Oncology 2019
Kim, J Hepatol 2019
Yip, J Hepatol 2019

Effect of Predniso(lo)ne Induction Dose on Remission in Autoimmune Hepatitis

- 30 or 60 mg prednisolone?
- Multicenter European retrospective study
- 451 patients
- Low dose (<0,5 mg/kg) vs high dose (>0,5 mg/kg)
- Normalization liver enzymes 6 months:

-64.7% vs 70.5%

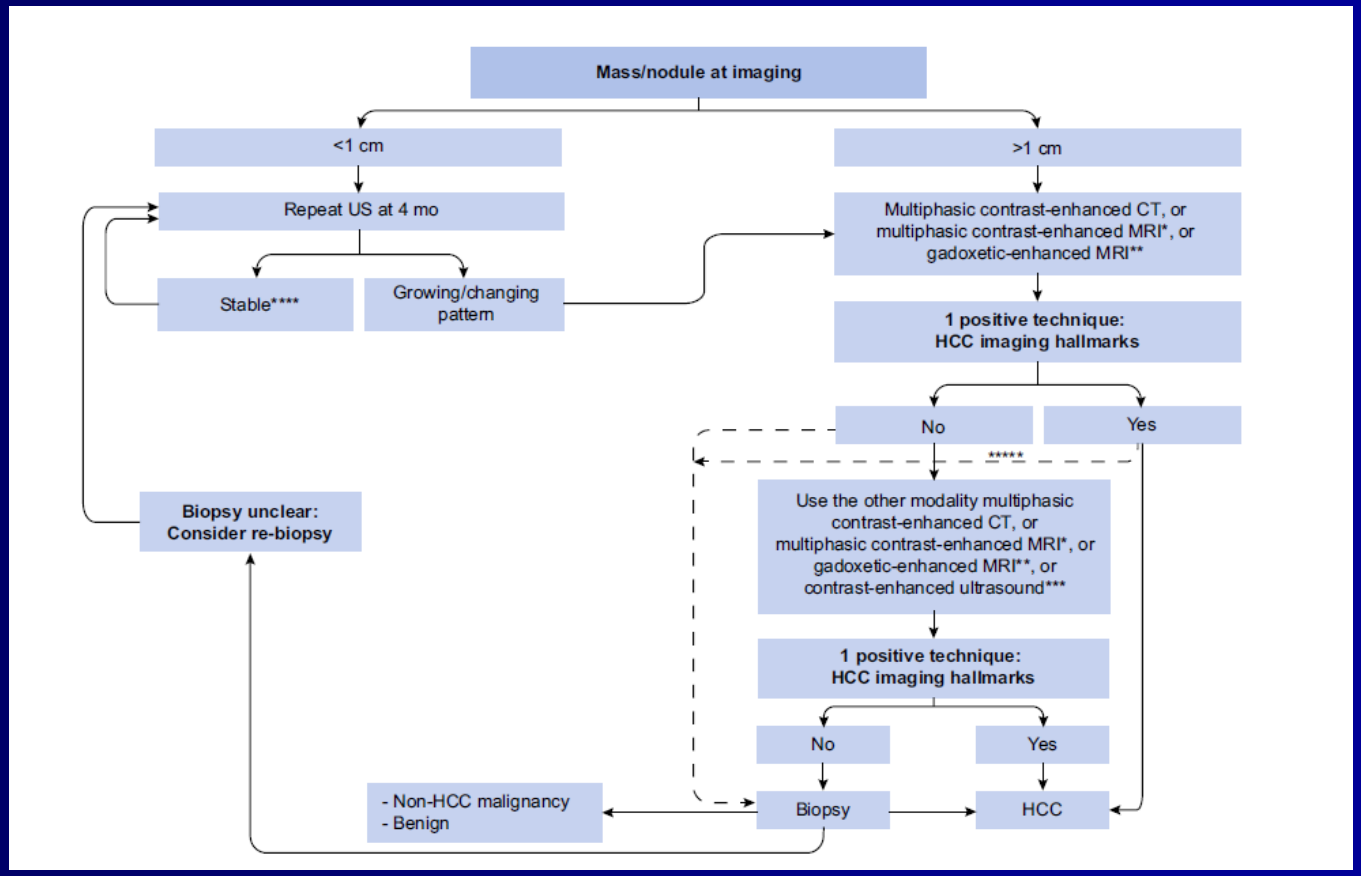
Pape, Clin Gastroenterol Hepatol 2019

Shorter Therapy Duration in Low-Risk Patients with Acetaminophen Overdose

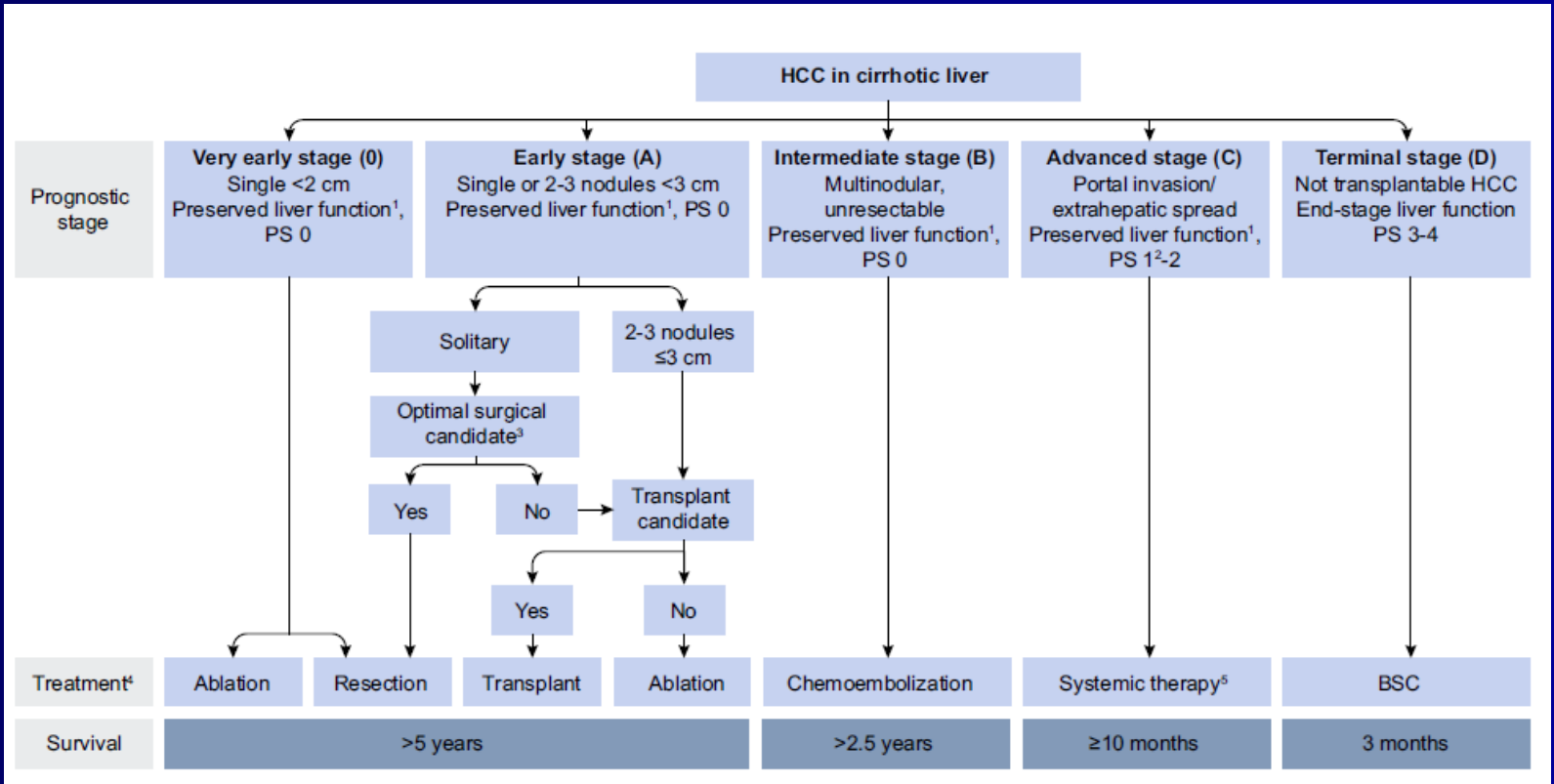
- N-acetylcysteine within 8 hours of acute acetaminophen overdose
- Multicenter, open label, Australia, 100 patients
- Normal ALT and Creatinine
- NAC 250/kg 12 hours vs 300/kg 20 hours
- Low acetaminophen levels, normal creatinine at 12h:stop NAC
- No Hepatic injury

Wong, Hepatology 2019

EASL 2018
Management of Hepatocellular Carcinoma



EASL 2018 Management of Hepatocellular Carcinoma



EASL Recommendations HCC and Evidence

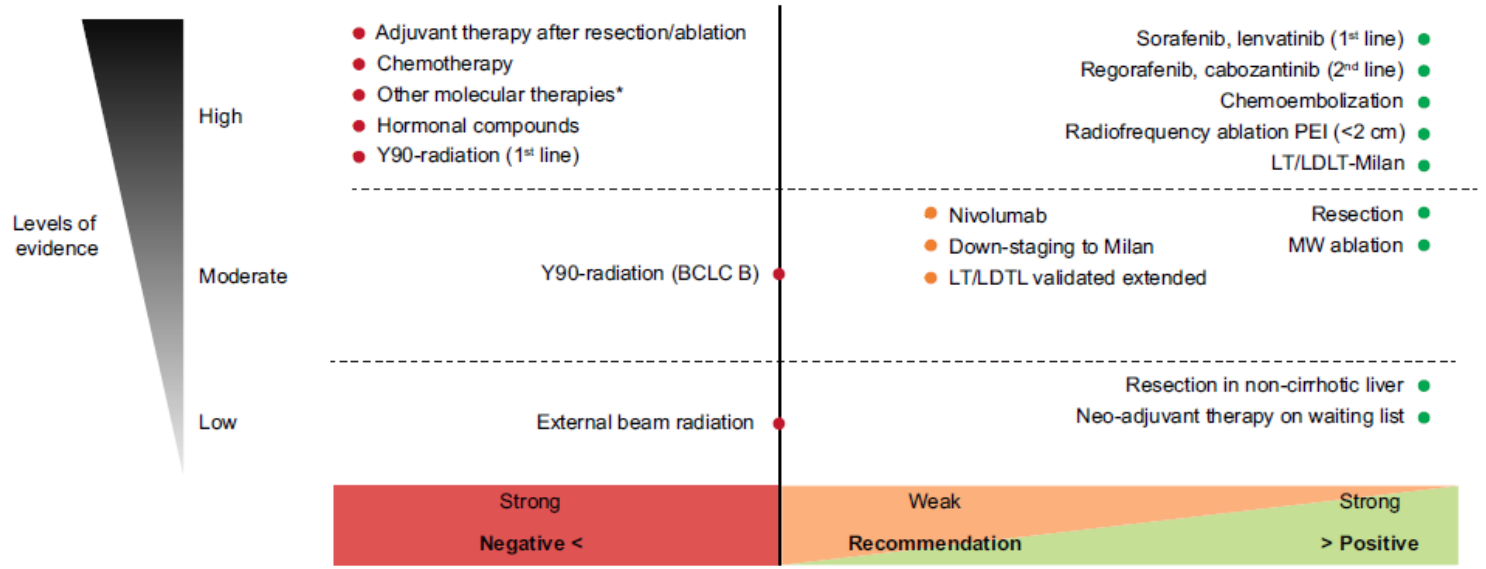
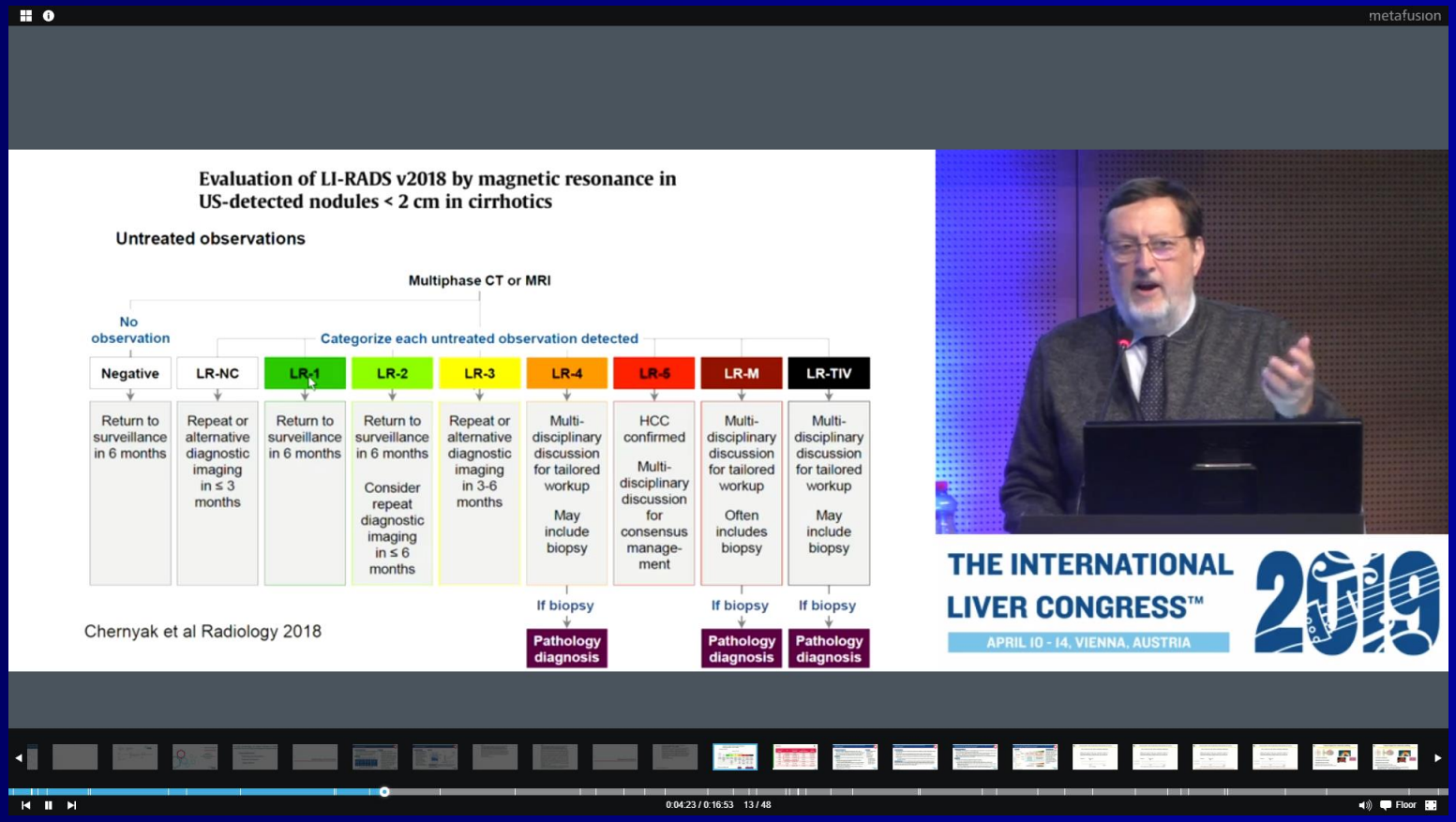
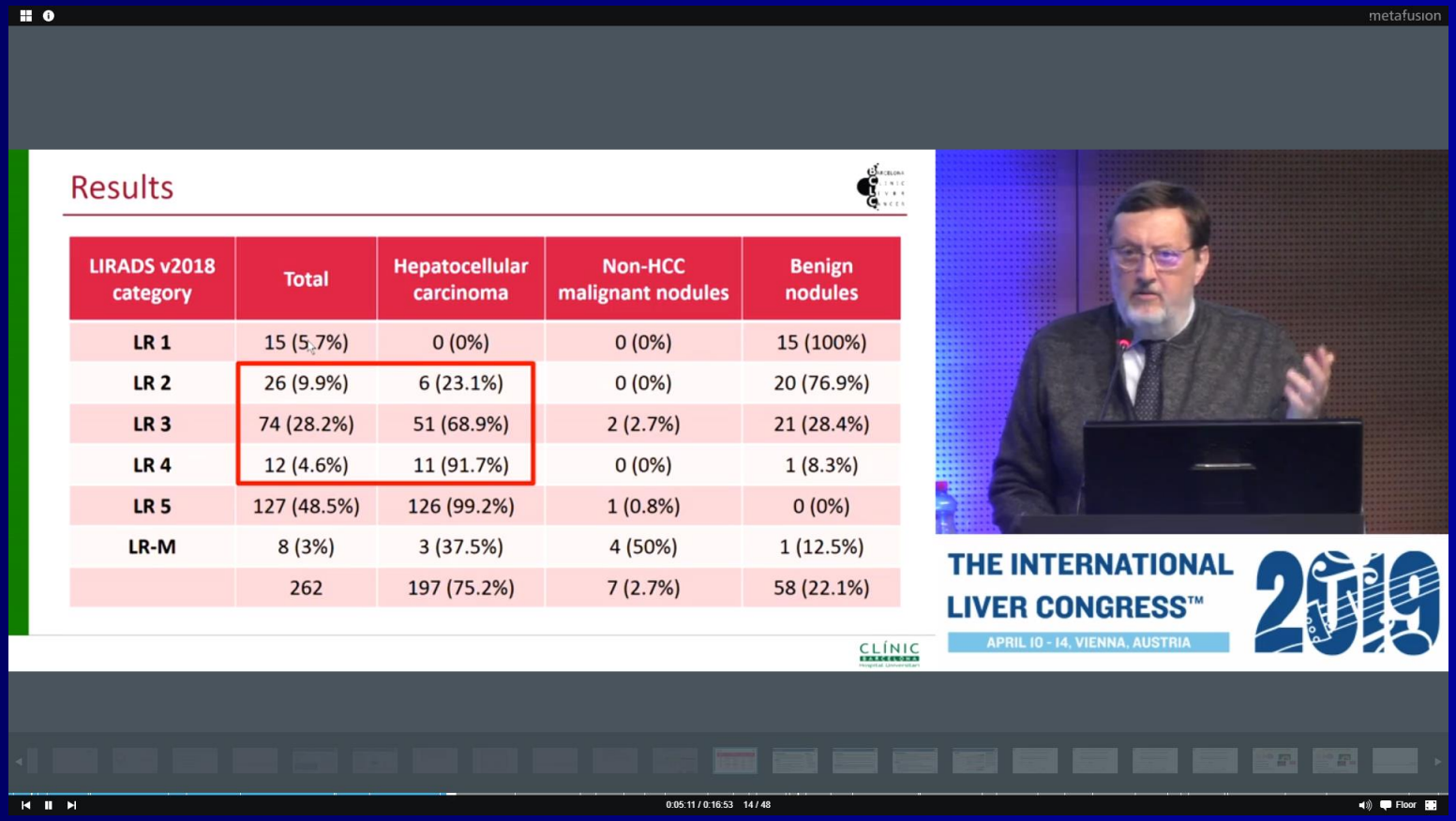


Fig. 9. Representation of EASL recommendations for treatment according to levels of evidence and strength of recommendation (adaptation of the GRADE system). LDLT, living donor liver transplantation; LT, orthotopic liver transplantation; MW, microwave; PEI, percutaneous ethanol injection; RF, radiofrequency ablation.

HCC Diagnosis: LI-RADs



HCC Diagnosis: LI-RADs
LR 2,3,4 and HCC risk management: biopsy or repeat imaging



Forner, ILC 2019

FDA approves Cyramza for second line therapy in patients with liver cancer and high AFP

- REACH 2, randomized control phase 3
- HCC, previous treatment with sorafenib
- AFP > 400
- Death: 75% vs 78%
- Overall Survival: 8.5 vs 7.3 months
- Overall Response Rate: 4.6% vs 1.1%

May 13, 2019

ΚΑΛΟ ΚΑΛΟΚΑΙΡΙ

«Μύτη», Ποσείδι, Χαλκιδική