

Best Practice Guidelines and Cochrane Reviews in Gastroenterology and Hepatology

Z. Bahreini, N. Deol, A. Rammal, and A. B. R. Thomson

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Adverse Events of Upper GI Endoscopy: ASGE Guidelines (Members of the Standard of Practice Committee, and published in *Gastrointestinal Endoscopy* 2012; 76: 707-717)

Antibiotics Prophylaxis: ASGE Guidelines (Members of the Standards of Practice Committee. *Gastrointestinal Endoscopy* 2015; 81(1): 81-89)

Endoscopy in Pregnancy and During Lactation: ASGE Guidelines (Members of the Standards of Practice Committee, *Gastrointestinal Endoscopy* 2012; 76: 18-24)

Removal of Foreign Bodies in the Upper Gastrointestinal Tract: ASGE Guidelines (Birk M, et al. *Endoscopy* 2016; 48(5):489-96)

ESOPHAGUS

GERD

Barrett Esophagus Quality Indicators for Treatment with Resection and Endoscopic Eradication Therapy: The Treat-BE Consortium (Wani S, et al. *Am J Gastroenterology* 2017; 112: 1032-1048)

Barrett Esophagus: ACG Guidelines (Shaheen NJ et al. *Am J Gastroenterol* 2016; 111: 30-50)

Gastroesophageal Reflux Disease: ACG Guidelines (Katz PO et al. *Am J Gastroenterol* 2013; 108: 308-328)

Laparoscopic (LAP) versus open transhiatal esophagectomy (OTE) for esophageal cancer (ECA) (Gurusamy KS, et al. *Cochrane Library. Cochrane Database of Systemic Reviews* 2016; 3. Art.No: CD011390)

Laparoscopic fundoplication [LFP] surgery versus medical management [MM] for gastroesophageal reflux disease (GERD) in adults (Garg SK and Gurusamy KS. *Cochrane Library. Cochrane Database of Systemic Reviews* 2015; 11. Art.No: CD003243)

Dysphagia

Botulinum toxin for upper esophageal sphincter dysfunction in neurological disorders (Regen J, et al. *Cochrane Library. Cochrane Database of Systemic Reviews* 2014; 5. Art.No: CD009968)

Dysphagia: Percutaneous endoscopic gastrostomy (PEG) versus percutaneous radiological gastrostomy (PRG) for swallowing disturbances (Yuan Y, et al. *Cochrane Library. Cochrane Database of Systemic Reviews* 2016; 2. Art.No: CD009198)

Nutrition: Percutaneous endoscopic gastrostomy (PEG) versus nasogastric tube (NGT) for adults with swallowing disturbances (Gomes JR, et al. *Cochrane Library. Cochrane Database of Systemic Reviews* 2015; 5. Art.No: CD008096)

Eosinophilic Esophagitis (EoE)

Recommendations for Diagnosis and Treatment of PPI-responsive Esophageal Eosinophilia (PPI-REE) and Eosinophilic Esophagitis (EoE): ACG Guidelines (Dellon ES, et al. *Am J Gastroenterol* 2013; 108: 679-692)



Motility

Achalasia: ACG Guidelines (Vaezi MF, et al. Am J Gastroenterol 2013; 108: 1238-1249)

Endoscopic pneumatic dilation (EPD) versus botulism toxin injection (BTX) in the management of primary achalasia (Leyden JE, et al. Cochrane Library. Cochrane Database of Systemic Reviews 2014; 12. Art.No: CD005046)

Cancer

Chemotherapy versus chemotherapy plus surgery for esophageal cancer (93% squamous, 7% adenocarcinoma) patient population esophageal cancer

Chinese Herbal Medicine for esophageal cancer (Chen X, et al. Cochrane Library. Cochrane Database of Systemic Reviews 2016; 1. Art.No: CD004520)

Esophageal Cancer (Sreedharan A, et al. Cochrane Library. Cochrane Database of Systemic Reviews 2011; 2. Art.No: CD005048)

Esophageal Cancer: NOGCA Guidelines (Allum WH, et al. Gut 2011; 60: 1449-1472)

Esophagectomy (Yuan Y, et al. Cochrane Library. Cochrane Database of Systemic Reviews 2014; 10. Art.No: CD008446)

Long-term proton pump inhibitor (PPI) use and the development of gastric pre-malignant lesions (Song H, et al. Cochrane Library. Cochrane Database of Systemic Reviews 2014; 12. Art.No: CD010623)

Non-surgical versus surgical treatment for esophageal cancer in patients with esophageal squamous cell cancer who respond to induction chemoradiotherapy, and who are fit for surgery (Best LMJ, et al. Cochrane Library. Cochrane Database of Systemic Reviews 2016; 3. Art.No: CD011498)

Preoperative chemotherapy for resectable thoracic esophageal cancer (ECA) (Kidane B, et al. Cochrane Library. Cochrane Database of Systemic Reviews 2015; 5. Art.No: CD001556)

Squamous 97% (Vellayappan BA, et al. Cochrane Library. Cochrane Database of Systemic Reviews 2017; 8. Art.No: CD010511)

STOMACH

Non-Variceal Upper Gastrointestinal Bleeding (UGIB)

Non-Variceal Upper Gastrointestinal Bleeding: ICUGBCG Guidelines (ICUGBCG. Barkan AN, et al. Ann Intern Med 2010; 152: 101-113; NICE: Dworzynski K, et al. BMJ. 2012; 344: e3412)

Tranexamic acid for [non-variceal] upper gastrointestinal bleeding (Bennett C, et al. Cochrane Library. Cochrane Database of Systemic Reviews 2014; 11. Art.No: CD006640)

Upper Gastrointestinal Bleeding (Marti-Carvajal AJ and Sola I. Cochrane Library. Cochrane Database of Systemic Reviews 2015; 6. Art.No: CD006007)

Dyspepsia

Dyspepsia (Boghossian TA, et al. Cochrane Library. Cochrane Database of Systemic Reviews 2017; 3. Art.No: CD011969)



Dyspepsia: ACG / CAG Guidelines (Moayyedi PM, et al. Am J Gastroenterol 2017; 112: 988-1013)

Functional Dyspepsia (Pinto-Sanchez MI, et al. Cochrane Library. Cochrane Database of Systemic Reviews 2017; 11. Art.No: CD011194)

Role of Upper Gastrointestinal Biopsy to Evaluate Dyspepsia in the Adult Patient in the Absence of Visible Mucosal Lesions: AGA Guidelines (Yang Y-X, et al. Gastroenterology 2015; 149: 1082-1087)

Gastric Cancer

Premalignant Gastric Lesions: Atrophic Gastritis and Gastric Intestinal Metaplasia: High Risk Lesions For Gastric Adenocarcinoma: ESGE / EHSO / ESP Guidelines (Dinis-Ribeiro M, et al. Endoscopy 2012; 44: 74-94)

Helicobacter pylori Infection / Peptic Ulcer Disease

Abdominal drainage versus no drainage post-gastrectomy for gastric cancer (Wang Z, et al. Cochrane Library. Cochrane Database of Systemic Reviews 2015; 2. Art.No: CD008788)

Diagnostic accuracy of endoscopic ultrasonography (EUS) for the preoperative locoregional staging of primary gastric cancer (Mocellin S and Pasquali S. Cochrane Library. Cochrane Database of Systemic Reviews 2015; 2. Art.No: CD009944)

Gastric Cancer: NOGCA Guidelines (Allum WH, et al. Gut 2011; 60: 1449-1472)

Helicobacter Pylori (H. Pylori) Infection In Adults: CAG / CHSG / Toronto Guidelines (Fallone CA, et al. Gastroenterology 2016; 151: 51-69)

Helicobacter pylori eradication for the prevention of gastric neoplasia (Ford AC, et al. Cochrane Library. Cochrane Database of Systemic Reviews 2015; 7. Art No: CD005582)

Laparoscopic venous open gastrectomy for gastric cancer (Best LMJ, et al. Cochrane Library. Cochrane Database of Systemic Reviews 2016; 3. Art.No: CD011389)

Molecular-targeted first line therapy for advanced gastric surgery (Song H, et al. Wang Z, et al. Cochrane Library. Cochrane Database of Systemic Reviews 2016; 7. Art.No: CD011461)

Peptic Ulcer Disease (Gurusamy KS and Pallari E. Cochrane Library. Cochrane Database of Systemic Reviews 2016; 3. Art.No: CD011523)

Periodontal therapy as adjunctive treatment for gastric Helicobacter pylori infection (Ren Q, et al. Cochrane Library. Cochrane Database of Systemic Reviews 2015; 5. Art.No: CD009477)

Sequential versus standard triple first-line therapy for Helicobacter pylori eradication (Nyssen OP, et al. Cochrane Library. Cochrane Database of Systemic Reviews 2016; 3. Art.No: CD011389)

Treatment of Helicobacter pylori Infection: ACG Guidelines (Chey WD, et al. Am J Gastroenterol 2017; 112: 212-238)

SMALL BOWEL

Celiac Disease

Diagnosis and Management of Celiac Disease: ACG / WGO Guidelines (Bai JC, et al. J Clin Gastro 2013; 47: 121-126; Rubio-Tapia A, et al. Am J Gastroenterol. 2013; 108(5): 656-676)



Small Bowel Bleeding

Diagnosis and Management of Small Bowel Bleeding: ACG Guideline (Gerson LB, et al. Am J Gastroenterol 2015; 110: 1265-87)

Intestinal Failure

Benign Chronic Intestinal Failure (CIF) in Adults: ESPEN Guidelines (Pironi L, et al., Clin Nutrition 2016; 35: 247-307)

Crohn disease

Algorithm for Induction Therapy in Pregnant Women with IBD: Toronto Consensus Statement (Nguyen GC, et al. Gastroenterology 2016; 150: 734-757)

Biological Therapy in IBD: WCG Guidelines (D'Haens GR, et al. Am J Gastroenterol 2011; 106: 199-212)

Crohn Disease: Azathioprine (AZA) and 6-mercaptopurine (6-MP) (Chande N, et al. Cochrane Library. Cochrane Database of Systemic Reviews 2016; 10. Art No: CD000545)

Crohn Disease: Glutamine (GLU) (Akobeng AK, et al. Cochrane Library. Cochrane Database of Systemic Reviews 2016; 2. Art No: CD007348)

Crohn Disease: Induction of remission (Lim WC, et al. Cochrane Library. Cochrane Database of Systemic Reviews 2016; 7. Art No: CD008870)

Crohn Disease: Low dose naloxone (LDN) (Segal D, et al. Cochrane Library. Cochrane Database of Systemic Reviews 2014; 2. Art No: CD0010410)

Crohn Disease: Methotrexate (MTX) (McDonald JWD, et al. Cochrane Library. Cochrane Database of Systemic Reviews 2014; 8. Art No: CD003459)

Crohn Disease: Ustekinumab (USTs monoclonal antibodies that target the p40 subunit of cytokine IL-12) (McDonald JK, et al. Cochrane Library. Cochrane Database of Systemic Reviews 2016; 11. Art No: CD007572)

Endoscopic scoring indices for evaluation of disease activity in Crohn disease (Khanna R, et al. Cochrane Library. Cochrane Database of Systemic Reviews 2016; 8. Art No: CD010642)

Maintenance of Crohn disease: Antibiotics / anti-tuberculosis therapy (ATbT) (Patton PH, et al. Cochrane Library. Cochrane Database of Systemic Reviews 2016; 7. Art No: CD000299)

Maintenance of Crohn disease: Azathioprine (AZA) or 6-mercaptopurine (6-MP) (Chande N, et al. Cochrane Library. Cochrane Database of Systemic Reviews 2015; 10. Art No: CD000067 and Gordon M, et al. Cochrane Library. Cochrane Database of Systemic Reviews 2014; 8. Art No: CD010233)

Maintenance of Crohn disease: Budesonide (BUD) 6 mg (Kaenzig ME, et al. Cochrane Library. Cochrane Database of Systemic Reviews 2014; 8. Art No: CD002913)

Maintenance of Crohn disease: Methotrexate (MTX) (Patel V, et al. Cochrane Library. Cochrane Database of Systemic Reviews 2014; 8. Art No: CD006884)

Maintenance of Crohn disease: Omega-3 (n=3) fatty acid (fish oil) (Lev-Tzion R, et al. Cochrane Library. Cochrane Database of Systemic Reviews 2014; 2. Art No: CD006320)

Maintenance of medically-induced remission in Crohn disease (Akobeng AK, et al. Cochrane Library. Cochrane Database of Systemic Reviews 2016; 9. Art No: CD003715)



Management of Crohn Disease After Surgical Resection: AGA Guidelines (Regueiro M, et al. Gastroenterology 2017; 152: 277-295)

Management of Inflammatory Bowel Disease in Pregnancy: Toronto Consensus Statements (Nguyen GC, et al. Gastroenterology 2016; 150: 734-757)

Medical Management of Hospitalized Patients with Acute Severe Ulcerative Colitis: The Toronto Consensus (Bitton A, et al. Am J Gastroenterol. 2012; 107(2): 179-94)

Preventive Care in IBD: ACG Guidelines (Farraye FA, et al. Am J Gastroenterol 2017; 111: 241-258)

The Role of Endoscopy in Inflammatory Bowel Disease (IBD): ASGE Guidelines (Shergill AK, et al. Gastrointestinal Endoscopy 2015; 81(5): 1101-20)

Use of Immunomodulatory and Anti-TNF- α Drugs in Crohn Disease Moderately Severe Inflammatory –Type: AGA Guidelines (Terdiman JP, et al. Gastroenterology 2013; 145: 1459-63)

Diarrhea

Acute Diarrhea (Lazzerini I and Wanzira H. Cochrane Library. Cochrane Database of Systemic Reviews 2016; 12. Art No: CD005436)

Acute Diarrheal Infections in Immunocompetent Adults (Not Including Clostridium Difficile Infection): ACG Guidelines (Riddles MS, et al. Am J Gastroenterol 2016; 111(5):602-22)

Hand washing to prevent diarrhea (Ejemot-Nwadiaro RI, et al. Cochrane Library. Cochrane Database of Systemic Reviews 2015; 9. Art No: CD004263)

Oral zinc in children (Lazzerini M and Wanzira H. Cochrane Library. Cochrane Database of Systemic Reviews 2016; 12. Art No: CD005436)

Treating and Preventing Acute Diarrhea (Gregorio GV, et al. Cochrane Library. Cochrane Database of Systemic Reviews 2016; 12. Art No: CD006519)

COLON

Colorectal Cancer (CRC)

Colonoscopy Surveillance after Normal Colonoscopy or after Screening Polypectomy: US-MSTF Guidelines – American and British Perspective (Lieberman DA, et al. Gastroenterology 2012; 143: 844-857)

Colorectal Cancer Screening: US-MSTF Guidelines (Rex DX, et al. Am J Gastroenterol 2017; 112: 1016-1031)

Diagnosis and Management of Colorectal Cancer (CRC) in Inflammatory Bowel Disease (IBD): AGA / ASGE Guidelines (Farraye FA, et al. Gastroenterology 2010; 138: 738-745; and Laine L, et al. Gastrointestinal Endoscopy 2015; 81: 489-501)

Fecal Immune Testing for Colorectal Cancer: ASGE, ACG, AGAI, and US-MSTF Consensus Statement (Robertson DJ, et al. Gastrointestinal Endoscopy 2017; 85: 2-21)

Optimizing Adequacy of Bowel Cleansing for Colonoscopy: US-MSTF / ASGE Guidelines (Johnson DA, et al. Gastroenterol 2014; 109, 1528-1545; and Saltzman JR, et al. Gastrointestinal Endoscopy 2015; 81: 781-794)



Quality Measures for an Acceptable Colorectal Cancer Screening and Surveillance Program: AGAI Guidelines (Fayad NF and Kahi CJ. Clin Gastroenterol Hepatol 2014; 12: 1973-1980)

Ulcerative Colitis

Endoscopy in Patients with Inflammatory Bowel Disease: ASGE Guidelines (Shergill AK, et al. Gastrointestinal Endoscopy 2015; 81: 1101-1121)

Histological Scoring Indices in Ulcerative Colitis (Mosli MH, et al. Cochrane Library. Cochrane Database of Systemic Reviews 2017; 5. Art No: CD011256)

Maintenance of remission (Timmer D, et al. Cochrane Library. Cochrane Database of Systemic Reviews 2016; 5. Art No: CD000478)

Medical Management of Non-hospitalized Patient with Mild / Moderate Ulcerative Colitis: The Toronto Consensus Guidelines (Bressler B, Marshall JK, et al. Gastroenterology 2015; 148: 1035-58)

Tolerability Cyclooxygenase 2 inhibitor for rheumatological manifestation of inflammatory bowel disease (Wang Y, et al. Cochrane Library. Cochrane Database of Systemic Reviews 2014; 10. Art No: CD007744)

Treatment and Prevention of pouchitis after ileal pouch-anal anastomosis (IPAA) for chronic ulcerative colitis (Singh S, et al. Cochrane Library. Cochrane Database of Systemic Reviews 2015; 11. Art No: CD001176)

Ulcerative Colitis Induction of remission: Biologicals and Health-related quality of life (Rosenfold G, et al. Cochrane Library. Cochrane Database of Systemic Reviews 2015; 12. Art No: CD011661)

Ulcerative Colitis Induction of remission: Etrolizumab (ETRO) (Rosenfold G, et al. Cochrane Library. Cochrane Database of Systemic Reviews 2015; 12. Art No: CD011661)

Ulcerative Colitis Induction of remission: Oral 5-aminosalicylic acid (5-ASA) and salazopyrine (SASP) (Wang Y, et al. Cochrane Library. Cochrane Database of Systemic Reviews 2016; 4. Art No: CD000543)

Ulcerative Colitis Induction of remission: Oral budesonide – MMX (B-MMX) (Sherlock ME, et al. Cochrane Library. Cochrane Database of Systemic Reviews 2015; 12. Art No: CD007698)

Ulcerative Colitis Induction of remission: Type I interferon (Wang Y, et al. Cochrane Library. Cochrane Database of Systemic Reviews 2015; 9. Art No: CD006790)

Ulcerative Colitis Induction of remission: Unfractionated (UFH) and low molecular weight heparin (LMWH) (Chande N, et al. Cochrane Library. Cochrane Database of Systemic Reviews 2015; 8. Art No: CD006774)

Ulcerative Colitis Induction of remission: Vedolizumab (VEDO) (Bickston SJ, et al. Cochrane Library. Cochrane Database of Systemic Reviews 2014; 8. Art No: CD007271)

Ulcerative Colitis Maintenance of remission: Methotrexate (MTX) (Wang Y, et al. Cochrane Library. Cochrane Database of Systemic Reviews 2015; 8. Art No: CD007560)

Venothrombosis (VTE) in Inflammatory Bowel Disease (IBD): CAG Guidelines (Nguyen GC, et al. Gastroenterology 2014; 146: 835-48)



Polyps

Chromoscopy versus conventional endoscopy for the detection of polyps of the colorectum (Brown SR, et al. Cochrane Library. Cochrane Database of Systemic Reviews 2016; 4. Art No: CD006439)

Combination chemotherapy versus single-agent chemotherapy during preoperative chemoradiation for resectable rectal cancer (Resende HM, et al. Cochrane Library. Cochrane Database of Systemic Reviews 2015; 10. Art No: CD008531)

Epidermal growth factor receptor (EGFR) inhibitors for metastatic colorectal cancer (Chan DLH, et al. Cochrane Library. Cochrane Database of Systemic Reviews 2017; 6. Art No: CD004047)

Follow-up strategies for patients treated for non-metastatic colorectal cancer (Jeffery M, et al. Cochrane Library. Cochrane Database of Systemic Reviews 2016; 11. Art No: CD002200)

Hereditary Gastrointestinal Cancer Syndromes: ACG, AGAI, US-MSTF and US-NCCN Guidelines (Giardiello FM, et al. Am J Gastroenterol 2014; 109: 1159-1179; Ladabaum U, et al. Gastroenterology 2015; 149: 783-813; Rubenstein JH, et al. Gastroenterology 2015; 149: 777-782; Syngal S, et al. Am J Gastroenterol 2015; 110: 223-262)

Laparoscopic (LTME) versus open total mesorectal excision (OTME) for rectal cancer (Vennex S, et al. Cochrane Library. Cochrane Database of Systemic Reviews 2014; 4. Art No: CD005200)

Large Non-Pedunculated Colorectal Polyps (LNPCPS): ACPGB / BSG / NICE Guidelines (Rutter MD, et al. Gut 2015; 64(12):1847-73)

Lynch Syndrome (LS) (Giardiello FM, et al. Am J Gastroenterol 2014; 109: 1159-79)

Non-metastatic Colorectal Cancer: Antimicrobial Prophylaxis (Nelson RL, et al. Cochrane Library. Cochrane Database of Systemic Reviews 2014; 5. Art No: CD001181)

Recurrent colorectal cancer and blood carcino-embryogenic antigen (CEA) levels for detecting recurrence of colorectal cancer (CRC) is influenced by the cut-off concentration which when reached will trigger further diagnostic investigation for possible CRC recurrence (Nicholson BD, et al. Cochrane Library. Cochrane Database of Systemic Reviews 2015; 12. Art No: CD011134)

Serrated Lesions of the Colorectum: Cleveland Guidelines (Rex DK, et al. Am J Gastroenterol 2012; 107: 1315-1329)

Serrated Polyps In Colorectum: BSG Statement (East JE, et al. Gut 2017; 0: 1-16)

Water Infusion versus air insufflation for colonoscopy (Hafner S, et al. Cochrane Library. Cochrane Database of Systemic Reviews 2015; 5. Art No: CD009863)

Diverticulitis

Acute Uncomplicated Diverticulitis (AUD): AGAI Guidelines (Stollman N, et al. Gastroenterology 2015; 149: 1944-49; and Strate LL, et al. Gastroenterology 2015; 149: 1950-76)

Mesalamine versus no mesalamine to prevent recurrence of colonic diverticulitis (Carter F, et al. Cochrane Library. Cochrane Database of Systemic Reviews 2017; 10. Art No: CD009839)



Ischemia

Colonic Ischemia (CI): ACG Guidelines (Brandt LJ, et al. Am J Gastroenterol 2015; 110: 18-44)

Disorders Of Gut-Brain Interaction (DGBI) (Schmulson MJ and Drossman DJ. J Neurogastroenterol Motil 2017; 23: 151-63)

Irritable Bowel Syndrome (IBS) (Ford AC, et al. Am J Gastroenterology 2014; 109 Suppl 1:S2-26)

IBS / CIC

Anti-psychotic-related Constipation (Every-Palmer S, et al. Cochrane Library. Cochrane Database of Systemic Reviews 2017; 1. Art No: CD011128)

Biofeedback (Woodward S, et al. Cochrane Library. Cochrane Database of Systemic Reviews 2014; 3. Art No: CD008486)

Chronic Idiopathic Constipation (CIC): ACG Monograph (Ford AC, et al. Am J Gastroenterology 2014; 109 Suppl 1:S2-26)

Constipation in pregnancy (Rungsiprakarn P, et al. Cochrane Library. Cochrane Database of Systemic Reviews 2015; 9. Art No: CD011448)

Palliative Care (Candy B, et al. Cochrane Library. Cochrane Database of Systemic Reviews 2015; 5. Art No: CD003448)

Prevention of postpartum constipation (Turawa EB, et al. Cochrane Library. Cochrane Database of Systemic Reviews 2015; 9. Art No: CD011625)

Sacral nerve stimulation (SNS) for fecal incontinence and constipation in adults (Thaha MA, et al. Cochrane Library. Cochrane Database of Systemic Reviews 2015; 8. Art No: CD004464)

Anorectal Bleeding

Anorectal Disorders: ASGE Guidelines (Appalaneni V, et al. Gastrointestinal Endoscopy 2010; 72: 1117-1123)

Lower GI Bleeding: ASGE Guidelines (Pasha S, et al. Gastrointestinal Endoscopy 2014; 79: 875-85)

Microscopic Colitis

Lymphocytic Colitis (Chande N, et al. Cochrane Library. Cochrane Database of Systemic Reviews 2017; 7. Art No: CD006096)

Microscopic Colitis: AGAI Guidelines (Nguyen GC, et al. Gastroenterology 2016; 150: 734-757)

Clostridium Difficile Infections (CDI)

Clostridium Difficile Infections (CDI) (Surawicz CM, et al. Am J Gastroenterol 2013; 108: 478-498)

Probiotics for the prevention of CDI (Goldenberg JZ, et al. Cochrane Library. Cochrane Database of Systemic Reviews 2017; 12. Art No: CD006095)



APPENDIX

Appendix (Acute lower abdominal pain in young women

Gaitan HG, et al. Cochrane Library. Cochrane Database of Systemic Reviews 2014; 5. Art No: CD009683)

Timing of appendectomy for appendiceal phlegmon (Cheng Y, et al. Cochrane Library. Cochrane Database of Systemic Reviews 2017; 6. Art No: CD011670)

GALLBLADDER

Gallstone Disorders: EASL / NICE Guidelines (EASL. J Hepatology 2016; 65: 146-181; NICE: www.nice.org.uk/guidance/cg1888, 2014)

PANCREAS

Acute Pancreatitis

Acute Pancreatitis (AP): ACG / AGA Guidelines (Tenner S, et al. Am J Gastroenterol 2013; 108: 1400-15; and Forsmark CE and Baillie J. Gastroenterology 2017; 132: 2022-44)

Inflammatory Pancreatic Fluid Collections: ASGE Guideline (Muthusany VR, et al. Gastrointestinal Endoscopy 2016; 83: 481-488)

Post-ERCP Complications: ASGE Guidelines (Anderson MA, et al. Gastrointestinal Endoscopy 2012; 75: 467-473)

Role of Endoscopy in Benign Pancreatic Disease: ASGE Guidelines (Chanrasekhara V, et al. Gastrointestinal Endoscopy 2015; 82: 203-247)

Chronic Pancreatitis

Chronic Pancreatitis (ASGE Guidelines. Gastrointestinal Endoscopy 2015; 82: 103-214)

Chronic Pancreatitis (CP): APA Guidelines (Conwell DL, et al. Pancreas 2014; 43: 1143-1162)

Hereditary Pancreatic Cancer (Giardiello FM, et al. Am J Gastroenterol 2014; 109: 1159-1179; Ladabaum U, et al. Gastroenterology 2015; 149: 783-813; Rubenstein JH, et al. Gastroenterology 2015; 149: 777-782; Syngal S, et al. Am J Gastroenterol 2015; 110: 223-262)

Autoimmune Pancreatitis

Autoimmune Pancreatitis (AIP) (Hart PA and Chari ST. Gastroenterology 2015; 149: 39-51)

Pancreatic Cyst

Cystic Lesions of the Pancreas: ASGE / AGA Guidelines (Muthusamy VR, et al. Gastrointestinal Endoscopy 2016; 84: 1-9; and Vege S, et al. Gastroenterology 2015; 148: 819-822)



LIVER

Alcoholic Liver Disease:

Alcoholic Liver Disease (ALD): AASLD / ACG AND EASL Guidelines (AASLD. O'Shea RS, et al. Hepatology 2010; 51: 307-328; ACG. O'Shea RS, et al. Am J Gastroenterol 2010; 105: 14-32; EASL. J. Hepatology 2012; 57: 399-420; Singh S, et al. Gastroenterology 2015; 149: 958-970)

Non-Alcoholic Fatty Liver Disease (NAFLD)

Non-Alcohol related fatty liver disease (NAFLD) (Lombarde R, et al. Cochrane Library. Cochrane Database of Systemic Reviews 2017; 3. Art No: CD011640)

Non-Alcoholic Fatty Liver Disease (NAFLD) Including Liver Transplantation: AASLD / BSG / BASL / NHS Blood and Transplant Guidelines (Chalasani N, et al. Hepatology 2012; 55: 2005-23; Newsome PN, et al. Gut 2012; 61: 484-500)

Non-Alcoholic Fatty Liver Disease (NAFLD): AASLD / EASD / EASL / EASO / NICE Guidelines (AASLD: Chalasani N, et al. Hepatology 2012; 55: 2005-2023; EASL-EASD-EASO Clinical Practice Guidelines. J Hepatology 2016; 64(6): 1388–1402; Ahmed A, et al. Clin Gastroenterol Hepatol 2015; 13: 2062-2070)

Non-Alcoholic Fatty Liver Disease (NAFLD): AASLD Guidelines (Chalasani N, et al. Hepatology 2012; 55: 2005-2023)

Hereditary Hemochromatosis (HH)

Hereditary Hemochromatosis: AASLD / EASL Guideline (Bacon BR, et al. Hepatology 2011; 54: 328-343; Please also see Pietrangelo A. Gastroenterology 2015; 149: 1240-1251; Sarigianni M, et al. Clin Gastroenterol Hepatol 2015; 13: 55-61; AASLD: Bacon BR, et al. Hepatology 2011; 54: 328-343; EASL: J Hepatology 2010; 53: 3-22)

Hereditary hemochromatosis (Buzzett E, et al. Cochrane Library. Cochrane Database of Systemic Reviews 2017; 3. Art No: CD011647)

Wilson Disease (WD)

Wilson Disease (EASL Guidelines. J Hepatology 2012; 56: 671-685)

Primary Biliary Cholangitis (PBC)

Primary Biliary Cholangitis (PBC): EASL Guidelines (EASL: J Hepatology 2017; 67: 145-172; AASLD: Lindor KD, et al. Hepatology 2009; 50: 291-308)

Primary Biliary Cholangitis (PBC): AASLD Guidelines (Lindor KD, et al. Hepatology 2009; 50: 291-308)

Primary Biliary Cholangitis (PBC) (Saffioti F, et al. Cochrane Library. Cochrane Database of Systemic Reviews 2017; 3. Art No: CD011648)

Primary Biliary Sclerosing Cholangitis (PSC) (Saffioti F, et al. Cochrane Library. Cochrane Database of Systemic Reviews 2017; 3. Art No: CD011343)

Primary Sclerosing Cholangitis (PSC)

Primary Sclerosing Cholangitis (PSC): ACG / AASLD Clinical Practice Guideline (Lindor KD, et al. Am J Gastroenterol 2015; 110: 646-59; and Chapman R, et al. Hepatology 2010; S1: 660-78;



Rizvi S, et al. Clin Gastroenterol Hepatology 2015; 13: 2152-2165; and Eaton JE, et al. Gastroenterology 2013; 145: 52: 521-536)

Vascular Disorders

Vascular Disorders of the Liver: AASLD Clinical Guidelines (DeLeve LD, et al. Hepatology 2009; 49: 1729-64)

HBV Infection

Booster Vaccination to prevent HBV Infection (Poorolajal J, et al. Cochrane Library. Cochrane Database of Systemic Reviews 2016; 6. Art No: CD008256)

Booster Vaccination to prevent HBV Infection (Sangkomkamhang US, et al. Cochrane Library. Cochrane Database of Systemic Reviews 2014; 11. Art No: CD007879)

HBV Infection Reactivation During Immunosuppressive Drug Therapy (Reddy RR, et al. AGA Institute Guideline. Gastroenterology 2015; 148: 215-219)

HBV Infection: EASL Guidelines (EASL Clinical Practice Guidelines. J Hepatology 2017; 67(2): 370-398)

Hepatitis B Viral (HBV) Infection (Mantzoukis K, et al. Cochrane Library. Cochrane Database of Systemic Reviews 2017; 3. Art No: CD011645)

Treatment of Chronic Hepatitis B Virus (HBV) Infection: AGAI / EASL Guidelines (EASL. J Hepatology 2012; 57: 167-85; Martin P, et al. Clin Gastroenterol Hepatol 2015; 13: 2071-87; Reddy RR, et al. Gastroenterology 2015; 148: 215-19; and Perrillo RP, et al. Gastroenterology 2015; 148: 221-44; Nguyen LH, et al. Clin Gastroenterol Hepatol 2014;12:1262-1266; Brahmania M, et al. Lancet Infect Dis. 2016;16(2):e10-21)

HCV Infection

Hepatitis C Viral (HCV) Infection (Kalafateli M, et al. Cochrane Library. Cochrane Database of Systemic Reviews 2017; 3. Art No: CD011644)

Peginterferon alpha 2a versus peginterferon in chronic HCV infection (Hauser G, et al. Cochrane Library. Cochrane Database of Systemic Reviews 2014; 2. Art No: CD005642)

Peginterferon plus ribavirin versus interferon plus ribavirin for chronic HCV infection (Hauser G, et al. Cochrane Library. Cochrane Database of Systemic Reviews 2014; 2. Art No: CD005441)

Treatment of HCV Infection: AASLD / CASL and EASL Guidelines (CASL. Myres RP, et al. Can J Gastroenterol Hepatol 2015; 29: 19-34; and 2012; 26:359-75; EASL. J Hepatol. 2017;66(1):153-194; and AASLD. Ghany MG, et al. Hepatology 2011; 54: 1433-42; and Hepatology 2009; 49: 1335-42; Webster DP, et al. Lancet. 2015 21;385(9973): 1124-35)

Drug-Induced Liver Injury (DILI)

Drug-Induced Liver Injury (DILI): ACG Guidelines (Chalasani NP, et al. Am J Gastroenterol 2014; 109(7):950-66)

Abnormal Liver Chemistries

Evaluation of Abnormal Liver Chemistries: ACG Guideline (Kwo PY, et al. Am J Gastroenterol 2017; 112: 18-35)



Acute Liver Failure (ALF)

Acute Liver Failure: AASLD Position Paper / AGAI Guidelines (Flamm SI, et al. Gastroenterology 2017; 152: 644-647; and AASLD: Lee WM, et al. Hepatology 2011; 55: 1-22)

Hepatic Encephalopathy (HE)

Hepatic Encephalopathy (HE): AASLD and EASL Clinical Practice Guidelines (Vilstrup H, et al. Hepatology 2014; 60: 715-735)

Autoimmune Hepatitis (AIH)

Autoimmune Hepatitis (AIH): AASLD Guidelines (Manns MP, et al. Hepatology 2010; 51: 1-31)

Autoimmune Hepatitis (AIH): EASL Guidelines (AASLD Guidelines: Manns MD, et al. Hepatology 2010; 51: 1-31; BSG Guidelines: Gleeson D and Heneghan M. Gut 2011; 60(12):1611-29; EASL Guidelines: J Hepatology 2015; 63: 971-1004; Vierling JM. Clin Gastroenterol Hepatol 2015; 13: 2088-2108)

Ascites

Management of Adult Patients with Ascites: AASLD and EASL Practice Guideline (Runyon BA, Hepatology 2013; 54: 1-27 and 1651-1653; and EASL Clinical Practice Guidelines. J Hepatology 2010; 53: 397-417)

Ectopic Varices (EV)

Gastroesophageal Variceal Hemorrhage in Cirrhosis AASLD / WGO Guidelines (AASLD / ACG: Garcia-Tsao G, et al. Hepatology 2007; 46: 922-938; AASLD: Garcia-Tsao G, et al. Hepatology 2017; 65: 310-335; WGO World Gastroenterology Organization 2014. Also please see Garcia-Tsao G and Bosch J. N Engl J Med 2010; 362: 823-832)

Portal Hypertensive Bleeding In Cirrhosis: AASLD and NICE Guidelines (AASLD Practice Guidance: Garcia-Tsao G, et al. Hepatology 2017; 65: 310-335 and NICE guideline 2016. www.nice.org.uk/guidance/ng50)

Hepatocellular Cancer (HCC)

Diagnostic Algorithm for Suspected HCC: AASLD / EASL and EORTC Guidelines (AASLD – Bruix J and Sherman M. Hepatology 2011; 53: 1020-1022; and Heimback JK, et al. Hepatology;67(1):358-380; EASL – EORTC J. Hepatol 2012; 56: 908-943)

Focal Liver Lesions (FLL): AGA Guidelines (Marrero JA, et al. Am J Gastroenterol. 2014;109(9):1328-47)

Liver Transplantation (LTx)

Enhanced Recovery Protocols for Major Upper Gastrointestinal Hepatic or Pancreatic Surgery (Bond-Smith G, et al. Cochrane Library. Cochrane Database of Systemic Reviews 2016; 2. Art No: CD011382)

Liver Transplantation (LT): EASL Guidelines (EASL Guidelines. J Hepatology 2016;64(2):433-485)



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The primary purpose of this publication is education. The author, editor and publisher acknowledges that the development of new material opens its way for possible errors – what is correct today might not be the standard of care tomorrow. Readers are advised to ensure that the doses of drugs which they use are in compliance with their country's product information, and that the use of any therapeutic agent, be it a pharmaceutical or a technology, should be guided by local guidelines. There is often a wide diversity of professional opinion. Guidelines from one country are not always congruent with another.

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Thank you

A. B. R. Thomson



CANMED OBJECTIVES

Medical Expert

The discussion of complex cases provides the participants with an opportunity to comment on additional focused history and physical examination. They would provide a complete and organized assessment. Participants are encouraged to identify key features, and they develop an approach to problem-solving.

The case discussions, as well as the discussion of cases around a diagnostic imaging, pathological or endoscopic base provides the means for the candidate to establish an appropriate management plan based on the best available evidence to clinical practice. Throughout, an attempt is made to develop strategies for diagnosis and development of clinical reasoning skills.

Communicator

The participants demonstrate their ability to communicate their knowledge, clinical findings, and management plan in a respectful, concise and interactive manner. When the participants play the role of examiners, they demonstrate their ability to listen actively and effectively, to ask questions in an open-ended manner, and to provide constructive, helpful feedback in a professional and non-intimidating manner.

Collaborator

The participants use the “you have a green consult card” technique of answering questions as fast as they are able, and then to interact with another health professional participant to move forward the discussion and problem solving. This helps the participants to build upon what they have already learned about the importance of collegial interaction.

Manager

The participants are provided with assignments in advance of the three day GI Practice Review. There is much work for them to complete before as well as afterwards, so they learn to manage their time effectively, and to complete the assigned tasks proficiently and on time. They learn to work in teams to achieve answers from small group participation, and then to share this with other small group participants through effective delegation of work. Some of the material they must access demands that they use information technology effectively to access information that will help to facilitate the delineation of adequately broad differential diagnoses, as well as rational and cost-effective management plans.

Health Advocate

In the answering of the questions and case discussions, the participants are required to consider the risks, benefits, and costs and impacts of investigations and therapeutic alliances upon the patient and their loved ones.

Scholar

By committing to the pre- and post-study requirements, plus the intense three day active learning Practice Review with colleagues is a demonstration of commitment to personal education. Through the interactive nature of the discussions and the use of the “green consult card”, they reinforce their previous learning of the importance of collaborating and helping one another to learn.



Professional

The participants are coached how to interact verbally in a professional setting, being straightforward, clear and helpful. They learn to be honest when they cannot answer questions, make a diagnosis, or advance a management plan. They learn how to deal with aggressive or demotivated colleagues, how to deal with knowledge deficits, how to speculate on a missing knowledge byte by using first principles and deductive reasoning. In a safe and supportive setting they learn to seek and accept advice, to acknowledge awareness of personal limitations, and to give and take 360° feedback.

Knowledge

The basic science aspects of gastroenterology are considered in adequate detail to understand the mechanisms of disease, and the basis of investigations and treatment. In this way, the participants respect the importance of an adequate foundation in basic sciences, the designing of clinical research studies to provide an evidence-based approach, the relevance of their management plans being patient-focused, and the need to add “compassionate” to the Three C’s of Medical Practice: competent, caring and compassionate.

“They may forget what you said, but they will never forget how you made them feel.”

Carl W. Buechner, on teaching.

“With competence, care for the patient. With compassion, care about the person.”

Alan B. R. Thomson, on being a physician.



PROLOGUE

Like any good story, there is no real beginning or ending, just an in-between glimpse of the passing of time, a peek into a reality of people's minds, thoughts, feelings, and beliefs. The truth, as I know, has a personal perspective which drifts into the soul of creation. When does life begin, when does an idea become conceived, when do we see love or touch reality? A caring, supportive, safe, and stimulating environment creates the holding blanket, waiting for the energy and passion of those who dream, invent, create – disrupt the accepted, challenge the conventional, ask questions with forbidden answers. Be a child of the 60's. Just as each of us is a speck of dust in the greater humanity, the metamorphosis of the idea is but a single sparkle in the limitlessness of the Divine Intelligence. We are the ideas, and they are us. No one of us is truly the only parent of the idea, for in each of us is bestowed the intertwined circle of the external beginning and the end....

...during a visit to the Division of Gastroenterology at the University of Ottawa several years ago, the trainees remarked how useful it would be to have more than two hours of learning exchange, a highly interactive tutorial with concepts, problem solving, collegial discussion, the fun and joys of discovery and successes. Ms. Jane Upshall of BYK Canada (Atlanta, Nycomed), who had sponsored two of these visiting Professorships, encouraged the possibility of the development of a longer program. Her successor, Lynne Jamme, supported the initial three-day educational event for the trainees enrolled in the GI training program at the University of Ottawa. With her entrepreneurial foresight, wisdom, and enthusiasm, the idea began. Lynne's commitment to an event which benefited many of the future clinicians, who will care for ourselves and our loved ones, took hold. Then, thanks to the GI program directors in Ottawa and the University of Western Ontario, Nav **Saloojee** and Jamie Gregor, more trainees were exposed, future GI fellows talked with other trainees, and a grass roots initiative began. Had it not been for Nav and Jamie's willingness to take a risk on something new, had they not believed in me, then there would have been no further outreach. Thank you, Lynne, Nav, and Jamie. You were there at the beginning. I needed you.

By 2008, all but one GI program in the country gave their trainees time off work to participate in the three-day event, GI Practice Review (GI-PR). The course is 90% unsponsored, and is gratis to the participants, (except for the cost of their enthusiastic participation!) I am happy to give back to the subspecialty that gave me so much for 33 years. I hope GI-PR is helpful to all trainees. I know that from these future leaders there will arise those who will continue to dedicate and donate their time, energy, and ability to the betterment of those who contribute to the continued improvement of our medical profession. The clinicians, the teachers, the researchers.

In a short span of eight years, more than 300 fellows, coming from all the 14 training programs in Canada, have participated in the small group sessions in the GI practice review. I thank the training program directors who have supported GI-PR. Special appreciation as well to their many staff physicians who worked without their trainees for the three days of each program.

The idea for the electronic and hard copy summary of the "list of facts" came from the trainees who wished for an aide memoir. But the GI-PR is about more than lists and facts - it is about problem formulation, case discussions, review of endoscopy, histopathology, motility, diagnostic imaging. It is about having fun working together to learn. The subterfuge to gain interest in the basic sciences is the use of clinical scenarios to show the way to the importance of first principles. While the lists are here, the experience is in the performance.



The child will grow, the images will expand, the learning of all aspects of our craft will develop and flourish amongst persons of good will. Examinations will become second nature, as each clinical encounter, each person, each patient, becomes our test, the determination of clinical competence, of caring, of compassion. May these three C's become part of each of our life's narrative. And from this start comes Capstone Academic Publishing, an innovation for the highest quality and value in educational material, made available at cost, speaking in tongues, in the languages of many cultures, with the dialect of the true North strong and free, so that knowledge will be free at last.

Outstanding medical practice and true dedication to those from whom we receive both a privilege and pleasure of care, comes from much more than the GI-PR can give you, much more than Q & As, descriptions of diagnostic imaging or endoscopy stills or videos, histopathology or motility. True, we need all of these to jump over a very high bar. But to be a truly outstanding physician, you need to care for and care about people, and you must respect the dignity and rights of all others. You must strike a balance between love and justice, and you place your family and friends at the top of your wish-list of lifetime achievements.

For the skeptics who ask "What do you want from me?" I simply say "You are the future; I trust that in time you too will help young people to be the best they can be."

May good luck, good health, modesty, peace, and understanding be with you always. Through medicine, all persons of the world may come to share caring, respect, dignity, and justice.

Sincerely,

Alan Thomson

Emeritus Distinguished University Professor, U of A

Adjunct Professor, Western University, London, Canada



ACKNOWLEDGEMENTS

Patience and patients go hand in hand. So also does the interlocking of young and old, love and justice, equality and fairness. No author can have thoughts transformed into words, no teacher can make ideas become behavior and wisdom and art, without those special people who turn our minds to the practical - of getting the job done!

Thank you, Naiyana, for translating those scribbles (called my handwriting), into the still magical legibility of the electronic age. Sarah, thank you for your hard work and creativity.

My most sincere and heartfelt thanks go to the excellent persons at JP Consulting, and CapStone Academic Publishers. Jessica, you are brilliant, efficient, dedicated, and caring. Thank you most sincerely.

When Rebecca, Maxwell, Megan, Henry, Felix, Toby, Grady and Jasper, ask about their Grandad, I will depend on James and Anne, Matthew and Allison, Jessica and Matt, and Benjamin to be understanding, generous, kind and forgiving. For what I was trying to say and to do was to make my professional life focused on the four C's and an "H"; competence, caring, compassion, and composure, as well as humor - and to make my very private personal life dedicated to family – to you all.



DEDICATION

تقديم به همه کسانی که پژواک صدای برابری طلبی جنسیتی در عرصه آموزش هستند و بی وقفه تلاش می کنند تا آینده ای را بسازند که در آن هر زن و دختر بتواند پرتوان زندگی کند

ਅਸੀਂ ਆਪਣਾ ਇਹ ਉੱਦਮ ਉਹਨਾਂ ਲੋਕਾਂ ਨੂੰ ਸਮਰਪਤਿ ਕਰਦੇ ਹਾਂ ਜਿਹਨਾਂ ਨੇ ਵੀਦਿਆ ਦੇ ਖੇਤਰ ਵਿੱਚ ਔਰਤ ਅਤੇ ਮਰਦ ਨੂੰ ਬਰਾਬਰ ਹੱਕ ਮਲਿਣ ਲਈ ਆਪਣੀ ਆਵਾਜ਼ ਉਠਾਈ ਅਤੇ ਲਗਾਤਾਰ ਇੱਕ ਅਜਿਹਾ ਭਵਿੱਖ ਸਰਜਣ ਦੀ ਕੋਸ਼ਿਸ਼ ਕੀਤੀ ਜਿਸ ਵਿੱਚ ਹਰ ਲੜਕੀ ਅਤੇ ਔਰਤ ਆਪਣਾ ਆਤਮ ਨਰਿਭਰ ਜੀਵਨ ਜਿਉਂ ਸਕੇ।

نحن نكرس هذا العمل لجميع أولئك الذين استخدموا صوتهم لتعزيز المساواة في الوصول إلى النوع الاجتماعي للتعليم الجيد ، والذين سعى
بلا هوادة لخلق مستقبل حيث
كل امرأة وفتاة يمكن أن يعيشوا حياة مفعلة

Nous dédions ce travail à tous ceux et celles qui ont utilisé leurs voix afin de promouvoir l'égalité des sexes dans l'accès à une éducation de qualité, et qui ont travaillé avec acharnement afin de créer un avenir où chaque fille et chaque femme est habilitée à mener une vie autonome et indépendante.

We dedicate this work to all those who have used their voice to promote equal gender access to quality education, and who have relentlessly strived to create a future where every woman and girl can live an empowered life.



ABBREVIATIONS OF NAMES OF PROFESSIONAL ASSOCIATIONS RECOMMENDED GUIDELINES SUMMARIZED HEREIN

A	AASLD	American Association for the Study of Liver Disease
	ACG	American College of gastroenterology
	ACPG	Association of Coloproctologists of Great Britain
	AGA	American Gastroenterology Association
	AGAI	American Gastroenterology Association Institute
	APA	American Pancreatic Association
	ASGE	American Society for Gastrointestinal Endoscopy
	ASPEN	American Society for Parenteral and Enteral Nutrition
B	BASL	British Association for the Study of the Liver
	BSG	British Society of Gastroenterology
C	CAG	Canadian Association of Gastroenterology
	CASL	Canadian Association for the Study of the Liver
	Cleveland Guidelines	
E	EASD	European Association for the Study of the Liver
	EHSG	European Helicobacter Study Group
	EORTC	European Organization for Research and Treatment of Cancer
	ESGE	European Society of Gastrointestinal Endoscopy
	ESP	European Society of Pathology
	ESPEN	European Society for Clinical Nutrition and Metabolism
I	ICUGBCG	International Consensus Upper Gastrointestinal Bleeding Conference Group
N	NHS	National Health Services
	NICE	National Institute of Health and Care Excellence
	NOGCA	National Oesophago-Gastric Cancer Audit
T	Toronto Consensus Group	
U	US-MSTF	United States Multi-Society Task Force
	US-NCCN	United States National Comprehensive Cancer Network
W	WCG	World Congress of Gastroenterology
	WHO	World Health Organization
	WOG	World Organization of Gastroenterology



CARMS TIPS

➤ Principles

- Be prepared, be early, be rested, dress for the occasion, and be yourself. “Sell” yourself – explain why will they be lucky to have you in their program?

➤ Role-play

- Tell me
 - About yourself
 - About yourself, not on CV
 - About your strengths/weaknesses and examples for each
 - People prepare for interviews by putting together stories about their experiences. Tell me a story
 - What were the quality of the people who were your mentors, medical, non-medical
 - Examples of what you do for
 - Fun
 - Reading outside medicine
 - Research
 - Community/social responsibility
 - Keeping up-to-date – medicine, outside of medicine (how will you be a “citizen of the world”?)
 - Practice giving an interview
 - Looking in the mirror
 - Recording your interview
 - Do a practice interview with a willing and experienced person
 - How have you resolved an ethical issue with a staff, coworker or difficult patient
 - Give me two examples of social injustice which you plan to improve in your position as physician
 - Let’s talk outside your comfort zone. Discuss for me, please:
 - People don’t always tell “the whole truth”. Give me 2 examples where you over- or understated facts in your CV or your answers today.
 - Do physicians make too much money?
 - When do physicians cheat?
 - How will we continue to pay for our health care system?
 - What do physicians mean when they say they have “no conflicts of interest”?
 - After a successful residency/fellowship, you will interview for a “real job”. Tell me what you will look for.
 - Tell me anything else that you would like me to know, or for me to tell you, that would make this a “number one-one” match.
 - There are certain things that I am not supposed to ask you on this interview. Are there any things that I have not asked you that you would like to tell me.

Heads-up

- Find out the NAMES of the interviewers: look up where they trained and what they have published recently
- Talk to ≥ 2 residents already in the program

Caution

- If you put down interests like reading, travel, you had better do your homework
- A recent book you have read in depth, and an author you know well
- Travel some place unusual, not Toronto / Vancouver

* Handout, Department of Medicine, Division of General Internal Medicine, Western University, London, ON; Dr. SheriLyne Kane, Program Director

➤ After the interviews

- Send a thank you letter to everyone you met, including other residents, secretaries, students, RNs.



LEADING CAUSES OF DEATH FROM GASTROINTESTINAL AND LIVER DISEASE (USA)

Rank	Cause of Death	No. of deaths		
		Underlying cause (x 10 ³)	Contributing cause (x 10 ³)	Crude rate (x 10 ⁵)
				The top 3
1	Colorectal / anal cancer	52	61	17
2	Pancreatic cancer	36	37	12
3	Liver and Intrahepatic Bile Duct Cancer	20	21	6
4	Fibrous / cirrhosis	15	31	5.0
5	Alcoholic liver disease	15	20	5.0
6	Esophageal cancer	14	16	4.5
7	Gastric cancer	11	12	3.7
8	Vascular disorders of the intestine	8	16	2.7
9	<i>Clostridium difficile</i> colitis	7	11	2.4
10	Gastrointestinal hemorrhage, unspecified	7	27	2.4
11	Chronic hepatitis C	7	16	2.3
12	Paralytic ileus and intestinal obstruction	6	15	1.9
13	Hepatic failure, unspecified	4	28	1.3
14	Acute pancreatitis	3	6	1.0
15	Ulcers (gastric / duodenal / peptic)	3	7	1.0
16	Diverticular disease	3	5	1.0
17	Malignant neoplasms of the gallbladder	2	2	0.7
18	Cholecystitis	2	3	0.7
19	Perforation of the intestine (non-traumatic)	2	5	0.7



GI DRUGS, PREGNANCY AND SAFETY

General

- Pregnancy
 - Very few medications known to be safe or dangerous....most are in-between
 - Must take into account safety of medication, need for medication, and existence of alternative
 - Cipro' is an example of a category C which is contraindicated in pregnancy, since alternatives are available
- Nursing
 - Most medications enter breast milk, and are thus classified as "use with caution"
 - Decision regarding use depends on need and alternative available
 - If a patient, needs a calcineurin-acting drug, ask patient to not breastfeed rather than trying another immune suppressant

FDA categories (this is an old system which is no longer used, except by physicians who find it to be useful)

- A: Negative human studies
- B: (Negative human studies + positive animal studies) or (no human studies and negative animal studies)
- C: Positive animal studies but none in humans
- D: Positive human studies but benefit may > harm
- X: Contraindicated in human d / t evidence of risk > benefit

Upper GI Tract: Dyspepsia

Name	FDA	Nursing
- Antacids (AA)	Ca and Mg AAs is OK Avoid Al AA	Ca AA is OK Avoid Mg and Al AAs
- H2RA	B	Use caution
- PPI	B	Use caution
- Gravol	B	Use caution
- Maxeran	B	Use caution
- Stemetil	C	Use caution
- Ondansetron	B	Use caution
- Erythromycin	B	Yes
- Cisapride	C-	Use caution
- Tegaserod	B	No
- Misoprostol	X	No
- Bismuth	No	No



- “Use caution” means the drug is excreted in breast milk, but benefit may exceed risk; consult Mother Risk.
 - If drug is not compatible with breastfeeding, consider pumping and discarding breast milk
- Note that “C” – means that it’s FDA acceptable, but on cross reference is not recommended

Abbreviations: AA, antacid; PPI, proton pump inhibitor

Lower GI Tract: Constipation

Name	FDA	Nursing
○ Fibre	Safe	Use
○ MOM	Safe	Use
○ Osmotic laxatives	Safe	Use
○ Sennokot, castor oil*	No	No
○ Amitriptyline	C	No

Abbreviation: MOM, milk of magnesia

* May trigger uterine contraction

IBD (Ulcerative Colitis, Crohn Disease)

Name	FDA	Nursing
○ Flagyl	B*	No
○ Ciprofloxacin	C but do not use in pregnancy	Use caution
○ Clavulin	B	Use caution
○ Sulphasalazine	B	Use caution
○ 5-ASA	B**	Use caution (possible risk of Reye syndrome)
○ Imuran / 6-MP	D	No
○ Methotrexate	X	No
○ IFX / Humira	B	Yes
○ Prednisone	C (cleft palate, neonatal AI)	Yes but do not breastfeed for 2 hr after taking
○ Heparin / LMWH	B	Yes
○ Tylenol	C	Yes
○ NSAIDs		Yes, but avoid ASA due to possible risk of Reye syndrome
○ Imodium	C-	Yes



Liver Disease

Name	FDA	Nursing
○ Cyclosporin	C	No
○ Tacrolimus	C	No
○ Sirolimus	C-	No
○ MMF	D	No
○ UDCA	B	No
○ IFN	C	No
○ Ribavirin	X	No
○ Nadolol	C-	Caution: Risk of neonatal hypoglycemia and bradycardia
○ Penicillamine	D	Caution***

* Avoid in first trimester (T1)

** Avoid ASAcol because of its content of phthalate

*** Do not suddenly stop treatment for Wilson disease for fear of precipitating acute liver failure, which must be treated by liver transplantation; consider preconception switch to triamterine or zinc

Abbreviations: IFN, interferon, UDCA, ursodeoxycholic acid; MMF, Mycophenolate Mofetil

Cirrhosis and Pregnancy

- Pregnancy is rare in cirrhosis
- Pregnancy occurs with non-cirrhotic portal hypertension
- ↑ risk of spontaneous abortion, prematurity, variceal bleeding due to ↑ blood volume and staining during delivery)
- Esophageal varices
 - Screen prior to pregnancy and band to eradication before conception
 - EGD at T2 (second third of pregnancy) if possible
 - Give good anesthesia at time of labour

Diagnostic Imaging

- Target exposure
 - Average 1 yr exposure: 360 mRad
 - Recommended radiation during gestation: < 500 mRad
 - Radiation dose needed for teratogenicity: > 5000 mRad
- Average radiation exposure (mRad)

○ Chest X-ray – 1	○ CT – 3000
○ Abdominal X-ray – 300	○ ERCP – 500
○ Barium enema – 1000	○ Gadolinium is avoided due to placental transfer
- In general, what is good for mother is good for baby, and you must seriously consider risk of missing an important GI diagnosis without appropriate imaging
- Remember to use good shielding for patient and for medical staff, who may also be pregnant and need protection



Endoscopy in Pregnancy and During Lactation: ASGE Guidelines

Abbreviation: ASGE, American Society for Gastrointestinal Endoscopy

Members of the Standards of Practice Committee, Gastrointestinal Endoscopy 2012; 76: 18-24

➤ Indications

“Invasive [including endoscopic] procedures during pregnancy are justified [only] when it is clear that failure to perform the procedure could expose the fetus and / or mother to harm”.

- Upper GI
 - Bleeding
 - Nausea / vomiting / abdominal pain
 - Dysphagia / odynophagia
- Lower GI
 - Severe unexplained diarrhea
 - Suspected colon cancer
- Hepatobiliary
 - Bile ducts
 - Choledocholithiasis
 - Duct injury
 - Pancreatitis (biliary origin)
- Pancreatic duct
 - Injury

➤ Contraindications

- Abruptio (placental abruption)
- Eclampsia, uncontrolled
- Expected (imminent) delivery
- Membranes ruptures

➤ Timing, positioning, duration

- Avoid endoscopic procedures in first term (T1)
- Left lateral or left pelvic tilt position
- Not a teaching case (i.e., experienced endoscopist, short procedure, lowest acceptable use of drugs for conscious sedation)

➤ Fetal monitoring

- < 24 wk
 - Doppler ultrasound to determine fetal heart rate before and after endoscopic procedure
- > 24 wk
 - Continuous electronic monitoring of fetal heart rate and uterine contractions by pediatric / neonatal specialists



➤ Drugs

- Sedation
 - None of the currently used anesthetic agents, when used in the standard concentrations at any gestational age, have any teratogenic effect in humans
 - Topical anesthetics
 - Meperidine is better than
 - Fentanyl, which is better than
 - Morphine
 - Propofol (trained / experience specialist)
 - If over-sedation results in
 - ↓ respiration
 - ↓ BP (hypotension)
 - ↓ LOC (loss of response / consciousness)
- } Naloxone
- Cathartics
 - Colonoscopy ▪ PEG (polyethylene glycol)
 - Sigmoidoscopy ▪ Tap water enemas

• Antibiotics

❖ Pregnancy

Safe	Contraindicated	Avoid in T1	Avoid in T3
○ Cephalosporins	– Quinolones	▪ Metronidazole	Nitrofurantoin*
○ Clindamycin	– Streptomycin		Sulfonamides
○ Erythromycin (but not estolate)			
○ Penicillins			

❖ Lactation

Safe	Contraindicated
○ Cephalosporines	– Ciprofloxacin
○ Erythromycin	– Ofloxacin
○ Nitrofurantoin*	– Sulfonamides
○ Penicillins	
○ Tetracycline	

* Note

- Do not give nitrofurantoin to patient with deficiency of glucose-6-phosphate dehydrogenase (G-6-PD)



Endoscopy

- Special risks
 - EGD and colonoscopy are generally safe, but only do if strong indication
 - Fetus very sensitive to maternal hypoxia or hypotension
 - Maternal positioning may impair IVC return
 - Unknown effects of maternal medication on fetus
 - Must balance risk of procedure with risk of not doing it (i.e., missed diagnosis)
- Medications
 - Propofol (B): preferred sedative
 - Demerol (B): preferred sedative
 - Fentanyl (C): preferred narcotic
 - Versed (D): associated with cleft palate
 - Narcan, flumazenil (C): can be used if needed
 - PEG: preferred colon cleanse (Pico-Salax may cause fluid shifts)
 - Water enema may be sufficient for flexible sigmoidoscopy
 - For breastfeeding mother, pump and discard milk for 24 hr after procedure, then resume breastfeeding
- Procedures
 - Accepted indications
 - Severe bleeding
 - Severe, refractory nausea / vomiting
 - Dysphagia, odynophagia
 - Severe diarrhea with negative work up
 - Biliary tract disease
 - Technical aspects
 - Perform in second trimester (T2)
 - Place in left-lateral position or use wedge under right hip
 - Ideally use propofol for anesthesia
 - Avoid abdominal pressure
 - Avoid cautery if possible (i.e., hemostasis, take off polyp after delivery)
 - Fetal monitoring
 - Obstetrical consultation



ENDOSCOPY ISSUES

Antibiotics Prophylaxis: ASGE Guidelines

Abbreviation: ASGE, American Society for Gastrointestinal Endoscopy

Members of the Standards of Practice Committee. Gastrointestinal Endoscopy 2015; 81(1):81-89.

❖ The High Risk Cardiac Patient

- Heart
 - Prosthetic mechanical or bioprosthetic cardiac valves
 - Cardiac transplantation recipients with cardiac valvulopathy
 - Congenital heart disease (CHO)
 - Cyanotic CHD
 - No repair
 - Repaired with prosthetic material / devices for first 6 mon after procedure
 - Repaired, but with residual defects
 - Previous history of infective endocarditis (IE)
- Infection
 - Already present in body
 - Situations where antibiotic prophylaxis indicated in non-cardiac patients
- Immunosuppression
 - Neutropenia (absolute neutrophil count < 500 cells/ μ L
 - Advanced hematological malignancies

} Consider individualize decision

❖ The Procedure

- ERCP
 - Incomplete drainage but no cholangitis
- EUS / FNA
 - For pancreatic / mediastinal cysts
- PEG / PEJ
 - Percutaneous endoscopic gastrostomy / jejunostomy placement of feeding tube
- Cirrhosis and GI bleeding (upper or lower)
 - EGD, colonoscopy
- Renal failure (peritoneal dialysis)
 - Colonoscopy

Abbreviations: EGD, esophagogastroduodenoscopy ERCP, endoscopic retrograde cholangiopancreatography; EUS, endoscopic ultrasound; FNA, fine needle aspiration;



- Use routine, single dose cephalosporin / penicillin-based prophylaxis.

- Choice of antibiotic
 - Directed against enterococci
 - Ampicillin
 - Penicillin
 - Piperacillin
 - Vancomycin
- The risk
 - Esophagus

		Dilation	~ 15% malignant > benign multiple dilators passed
 - Stomach (EGD)

4%	Sclerotherapy EV (esophageal varices)	~ 15%
 - Colon

- Diagnostic	4%		
- Therapeutic	6%	Endoscopic band ligation (EBL)	9%
 - Pancreas / biliary
tree (ERCP)

	No obstruction (no sphincterostomy, no stent)	6%

- Further guidelines and guidance

- Obtaining valid consent for endoscopic procedure (Everett SM, et al. Gut 2016; 65(10):1585-1601)

Ethical issues vary with the context, and in medicine such matters have pillars such as do

- Good
- No harm
- Fairly
- Openly

The ways to accomplish this are influenced by the community and the laws in place. For a perspective from the United Kingdom, please see the dose guidelines

- Anti-coagulation and antiplatelet therapy for endoscopic procedures (Veitch Am, et al. Gut 2008; 57: 1322-1329)
- Iron deficiency anemia (Goddard AF, et al. Gut. 2011;60(10):1309-1316)
- Chronic gastrointestinal problems arising as a result of treatment for cancer (Andreyev HJN, et al. Gut 2012; 61:179-182)
- Transition of GI care for paediatric to adult services (Brooks AJ, et al. Gut. 2017; 66(6): 988-1000)

Please refer to above for details regarding how to establish a Structural Transition Program to enhance the care of adolescent and young persons with chronic digestive disease to programs caring for adults.



Adverse Events of Upper GI Endoscopy: ASGE Guidelines

Abbreviation: ASGE, American Society for Gastrointestinal Endoscopy

Members of the Standard of Practice Committee, and published in Gastrointestinal Endoscopy 2012; 76: 707-717.

Please also see Kheraj R, et al. Clin Gastroenterol Hepatol 2012; 10: 1305-1314.

➤ Esophagogastroduodenoscopy (EGD)

❖ Diagnostic

- Bleeding (MW tear) 500 / 10⁵
- Cardiopulmonary 10-500 / 10⁵
- Endocarditis, infections 8%
- Perforation 10-40 / 10⁵
 - Mortality rate 2-36%

- EGD safe
 - No biopsy, platelets > 20,000/mL
 - Biopsy, platelets > 50,000/mL

❖ Therapeutic

- Dilation
 - Overall 0.1-0.4%
 - Strictures
 - Complex* 2-10%
 - Malignant 10%
 - Bacteremia (not clinically significant) 12-22%
 - Achalasia (pneumatic dilation) 2-8%
 - Gastric outlet obstruction 7%
 - Foreign body removal ~4%

* Mallory dilations, strictures many, long, angulated

➤ Percutaneous endoscopic gastrostomy (PEG) / Jejunostomy (PEJ)

- PEG
 - Placement 5-10%
 - Serous AEs 2 – 9%
 - Mortality 0.5^
 - 30 day all-cause mortality ~15%
 - Peristomal infection 26%
 - Pneumoperitoneum (benign) 12-38%

➤ Endoluminal resection

- EGD
 - Early
 - Late (delayed) 3-22%

} Pain / dyspepsia
Dysphagia / odynophagia



- EMR
 - Bleeding, perforation, stricture*
 - 0.5-5%
- ESD
 - Bleeding 11%
 - Perforation 6%
 - Pneumomediastinum (asymptomatic, benign) 31%
- Ablation
 - APC
 - Stricture, 6%; bleeding, 4%; perforation, 2%
 - PDT
 - Photosensitivity, 10-60%; esophageal stricture, 11-42%
- Cryotherapy
 - Strictures 4-10%
- Stents (self-expanding, metal)
 - Early, 2-12%
 - Late (delayed), 20-40%

* ↑ rate of stricture with ↑ mucosal resection

➤ Endoscopic variceal hemostasis

- Endoscopic variceal sclerotherapy
 - Overall, 35-78%
 - Mortality rate 1-5%
 - Ulceration 50-78%
 - Bleeding
 - Early 6%
 - Late (delayed) 19-24%
 - Intramural hematoma ~ 2%
 - Stricture 20%
 - Perforation 0.5-5%
 - Aspiration pneumonia 5%
 - Bacterial infection (cirrhotics) 50%
- Endoscopic band ligation (EBL)
 - Ulceration 5-15%
 - Aspiration 1%
 - Bacterial infection 4%

➤ Non-variceal hemostasis

- Overall major AEs 0.5%
- Perforation* 2%
- Bleeding (initiation, or exacerbation) 5%

* Higher rates ($\leq 4\%$ with repeated heater probing within 24-48 hr)

➤ Small Bowel Enteroscopy (aka Deep Enteroscopy, including double-balloon enteroscopy [DBE])

- Diagnostic
 - Major AEs 0.7%
 - Minor AEs 9%
- Therapeutic
 - 4%
 - Polypectomy 11%
 - Abdominal pain 20%
 - Pancreatitis 0.5%



ESOPHAGUS



- The Guidelines represent a consensus of best practice based on the available evidence at the time of preparation.
 - They might not apply in all situations and should be interpreted in the light of specific clinical situations and resources availability
 - Further controlled clinical studies may be needed to clarify aspects of these statements, and revision may be necessary as new data appear.
- Clinical considerations may justify a course of action at variance with these recommendations.
 - Guidelines are intended to be an educational device for providing information that may assist endoscopists in providing care to patients.
 - They are not rules and should not be construed as establishing a legal standard of care or as encouraging, advocating, requiring, or discouraging any particular treatment.

Birk M, et al. ECG Clinical Guideline. Endoscopy 2016; 48(5): 489-96.

“Life isn't about waiting for the storm to pass. It's
about learning how to dance in the rain...”

Vivian Greene



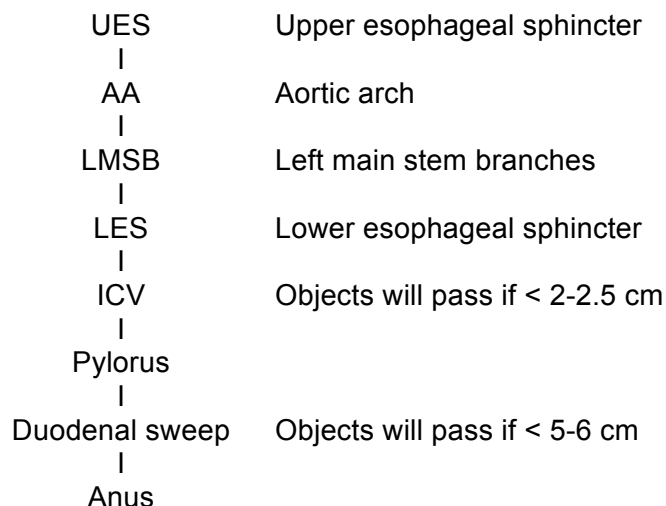
FOOD BOLUS OBSTRUCTION

Removal of Foreign Bodies in the Upper Gastrointestinal Tract: GSGE Guidelines

Birk M, et al. Endoscopy 2016; 48(5):489-96

➤ Anatomy

- Give the sites of physiological narrowing where ingested foreign bodies may become impacted or perforated.



➤ Clinical

- Asymptomatic
 - Small blunt objects (< 2-2.5 cm)
 - Short (< 5 – 6 cm)
 - Risk of perforation is ~25%
 - Treat within 24 hr
 - Body packing of drugs
 - Remove from esophagus within 2-5 hr, and from stomach within 24 hr
 - Batteries, magnets
- Symptoms
 - Wide, long, sharp (risk of complication 35%)
 - Complete obstruction
 - Incomplete obstruction
 - Endoscopic removal within 24 hr
 - Body packing
 - Obstruction, rupture → surgery
 - The area of retrosternal discomfort does not correlate with area of obstruction / impaction
 - Suspect complete obstruction of esophagus
 - ↑ salivation
 - ↓ ability to swallow saliva / fluids



- Suspect perforation
 - Vital signs
 - Fever, tachycardia, hypotension
 - Neck
 - Swelling crepitus
 - Chest
 - Wheeze, aspiration changes
- Diagnostic imaging
- ❖ Plain abdominal x-ray of neck, chest, abdomen
 - Induction
 - If bony food bolus suspected, but perforation not suspected
 - Perform plain film examination
- ❖ CT scan
 - Negative abdominal film, or
 - Perforation suspected
 - Negative abdomen radiography → CT scan
 - False-negative
 - Foreign body 50%
 - Food bolus ~90%
 - Fish bones 70%
- ❖ Barium swallow
 - Not recommended
 - Sensitivity >90%
 - Specificity ~95%
- ❖ Gastrografin swallow
 - If esophageal obstruction is considered, but urgent EGD should not be delayed
- Risk of perforation
 - Sharp object
 - 35%
 - Long object
 - > 5- 6 cm 25%
 - Bottom / small disk batteries
 - Risk of coagulation necrosis
 - Electrical discharging
 - Chemical injury
 - Electrical burns

}

↗

↘

Perforation

Fistula

 - Leakage of alkaline material / heavy metal poisoning
 - If foreign body stays in stomach for > 3- 4 wk, remove endoscopically!



➤ Endoscopic treatment

- Food bolus impaction
 - Endotracheal intubation if high risk of aspiration
 - Gently push bolus into stomach (right side of the bolus)
 - 90% of effective
 - Break apart large bolus
 - Extraction device +/- overtube / sheath, where appropriate
 - Inspect EGD for associated mucosal disease
 - Esophageal peptic strictures 80%
 - Eosinophilic esophagitis
 - Esophageal motility abnormality
 - Cancer

- Endoscopic methods to assure treat foreign body/food bolus
 - Success 95%
 - Complications 0% to 5%

MCQ Trick

- Glucagon has a poor efficacy to help pass food bolus, and in the presence of impaction, may ↑ risk of perforation/aspiration

➤ Follow-up

- Successful endoscopic management
 - Ensure EGD excluded associated disease in mucosa of esophagus, stomach, duodenum
- Unsuccessful endoscopic management
 - Long, sharp, wide: batteries, magnets, consider surgical removal
 - For all else (e.g., small coin)
 - Regulated radiographic follow-up until object pass in stool

“Having potential is great if you’re 12.”

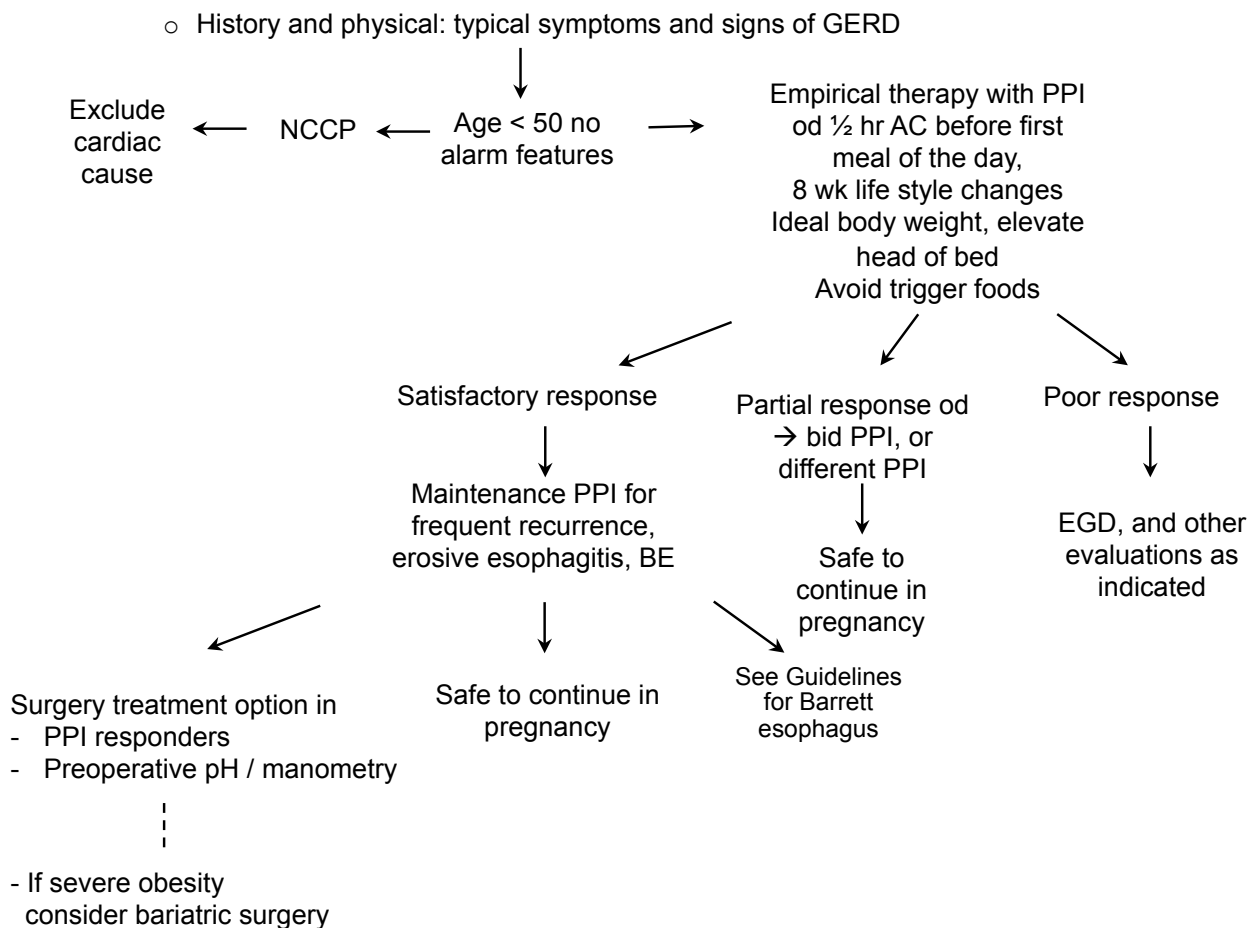
The Economist



GASTROESOPHAGEAL REFLUX DISEASE (GERD): ACG GUIDELINES

Abbreviations: ACG, American College of Gastroenterology

Katz PO et al. Am J Gastroenterol 2013; 108: 308-328.



Abbreviations: BE, Barrett esophagus; GERD, gastroesophageal reflux disease; NCCP, non-cardiac chest pain

"You have to put the puck in the net."

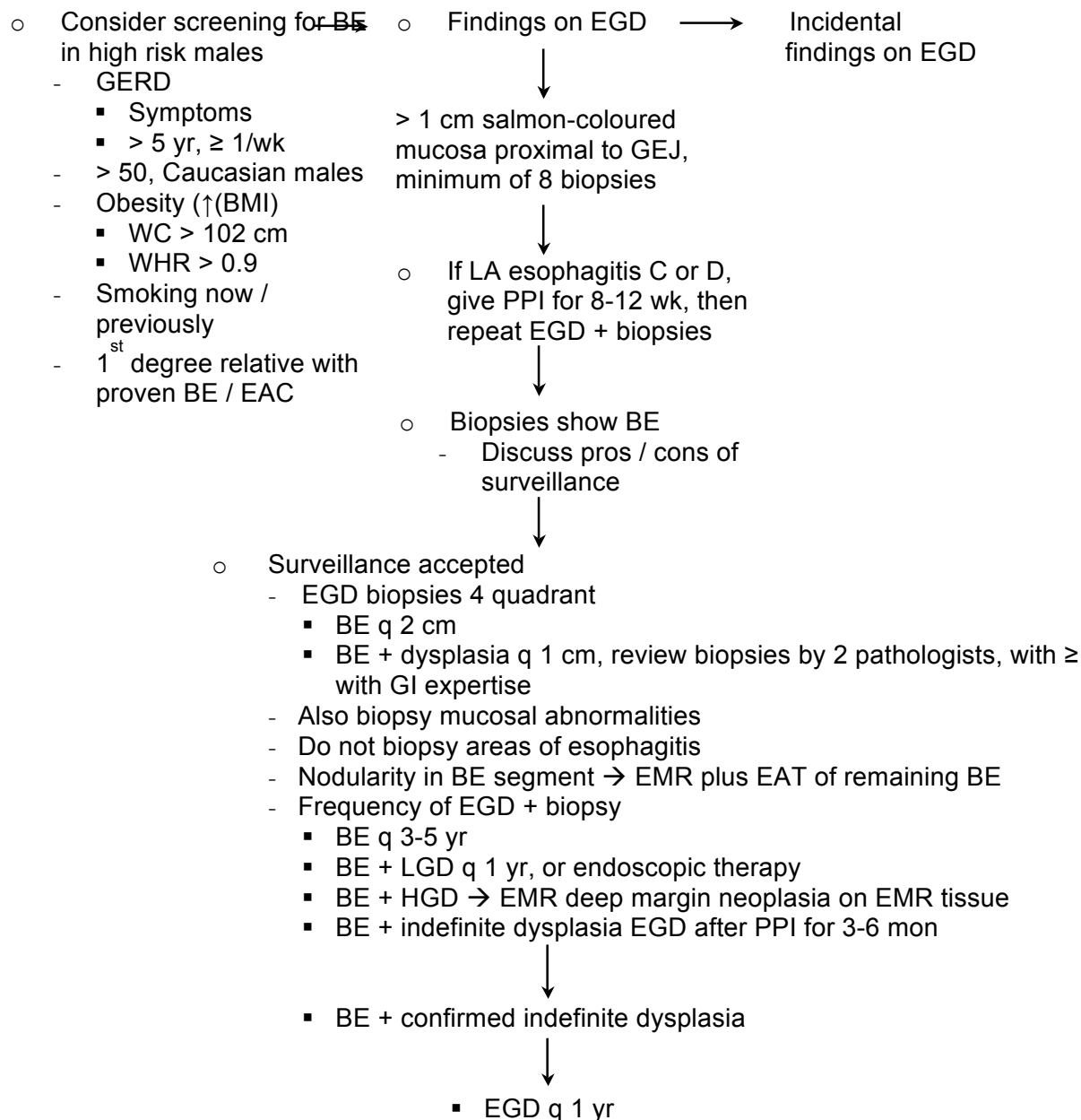
PW Armstrong

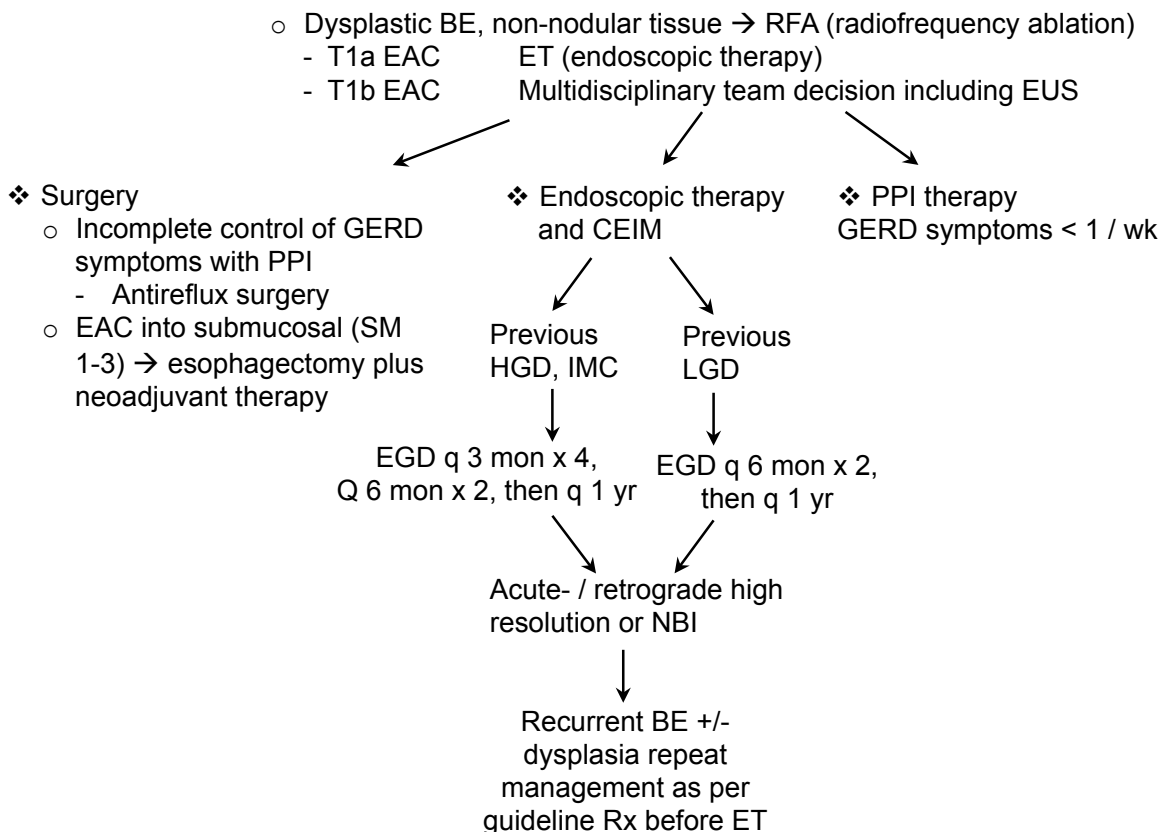


BARRETT ESOPHAGUS (BE): ACG GUIDELINES

Abbreviations: ACG, American College of Gastroenterology

Shaheen NJ et al. Am J Gastroenterol 2016; 111: 30-50.





Abbreviations: BE, Barrett esophagus; CEIM, complete elimination of intestinal metaplasia; EAC, esophageal adenocarcinoma; EGD, esophagogastroduodenoscopy; EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection; ET, endoscopic therapy; EUS, endoscopic ultrasound; GERD, gastroesophageal reflux disease; HGD, high-grade dysplasia; IMC, intramucosal carcinoma; LGD, low-grade dysplasia; PPI, proton pump inhibitor

"Always do your best. What you plant now, you will harvest later."

Og Mandino



Barrett Esophagus Quality Indicators for Treatment with Resection and Endoscopic Eradication Therapy: The Treat-BE Consortium

Wani S, et al. Am J Gastroenterology 2017; 112: 1032-1048.

- Pre-procedure
 - Endoscopy
 - Trained endoscopist experienced in mucosal ablation and endoscopic mucosal resection
 - Available high-definition white light endoscopy
 - Documentation of consent options, risks and benefits
 - Use of Prague grading system for description of BE
 - Pathology
 - Review endoscopic esophageal mucosal biopsies by at least two experienced GI pathologists
 - Use of Vienna classification
 - Negative for neoplasia +/- dysplasia
 - Indefinite for neoplasia +/- dysplasia
 - Non-invasive low-grade neoplasia (low-grade adenoma +/- dysplasia)
 - Non-invasive high-grade neoplasia (high-grade adenoma +/- dysplasia, non-invasive carcinoma and suspicion of invasive carcinoma)
 - Invasive neoplasia (intramucosal carcinoma, submucosal carcinoma, or beyond)
- Intra-procedure
 - Document the rate of use of quality indicators
 - Prague grading system of extent of BE abnormal mucosa seen on EGD
 - Use of appropriate ablation procedures
 - Visible lesions / lesions for targeted biopsied / removed en bloc or piecemeal
 - Optical chromendoscopy
- Post-procedure
 - After complete eradication of intestinal metaplasia (CE-IM)
 - Indicate defined intervals for repeat EGD plus biopsies (endoscopic surveillance)
 - Record distance from incisors to new squamocolumnar junction, using HD-WLE / optical chromendoscopy
 - Take biopsies from visible mucosal abnormalities
 - Complete the eradication of dysplasia / intramucosal cancer
 - Document adverse events
 - Treat symptoms of GERD with PPI

Abbreviations: BE, Barrett esophagus; CE-IM, complete eradication of metaplasia; CE-N, complete eradication of neoplasia; EGD, esophagogastroduodenoscopy; GERD, gastroesophageal reflux disease; HD-WLE, high-definition white light endoscopy; PPI, proton pump inhibitor



ESOPHAGEAL EOSINOPHILIA (EE) AND EOSINOPHILIC ESOPHAGITIS (EOE)

Recommendations for Diagnosis and Treatment of PPI-responsive Esophageal Eosinophilia (PPI-REE) and Eosinophilic Esophagitis (EoE) : ACG Guidelines

Abbreviations: ACG, American College of Gastroenterology

Dellon ES, et al. Am J Gastroenterol 2013; 108: 679-692.

➤ Clinical suspicion

- Esophageal symptoms (including food bolus impaction), atopy (e.g., reactive airway disease), plus 2-4 mucosal biopsies of mucosa of proximal and distal esophagus at EGD



- Pathological confirmation of esophageal eosinophilia ≥ 15 eosinophils per high power field (hpf) (EE)



- 8 wk course of proton pump inhibitors (PPI)



- Repeat EGD plus biopsies (regardless of symptomatology) improvement



- Persistence of esophageal eosinophilia (> 15 eosinophils/hpf)

Yes

PPI-REE taper / resume PPI as needed



- Clinicopathological and PPI failure compatible with eosinophilic esophagitis (EoE)



- Corticosteroids po
- Locally acting
 - Budesonide
 - Fluticasone



Poor response after 8 wk



- Corticosteroid (CS)
 - Topical CS continued
 - Systemic prednisone
- Elimination diet
- Endoscopic dilation (strictures non-responsive to CS or dilation)

Abbreviations: CS, corticosteroids; EE, esophageal eosinophilia; EDG, esophagogastroduodenoscopy; EoE, eosinophilic esophagitis; PPI-REE, proton pump inhibitor-responsive esophageal eosinophilia

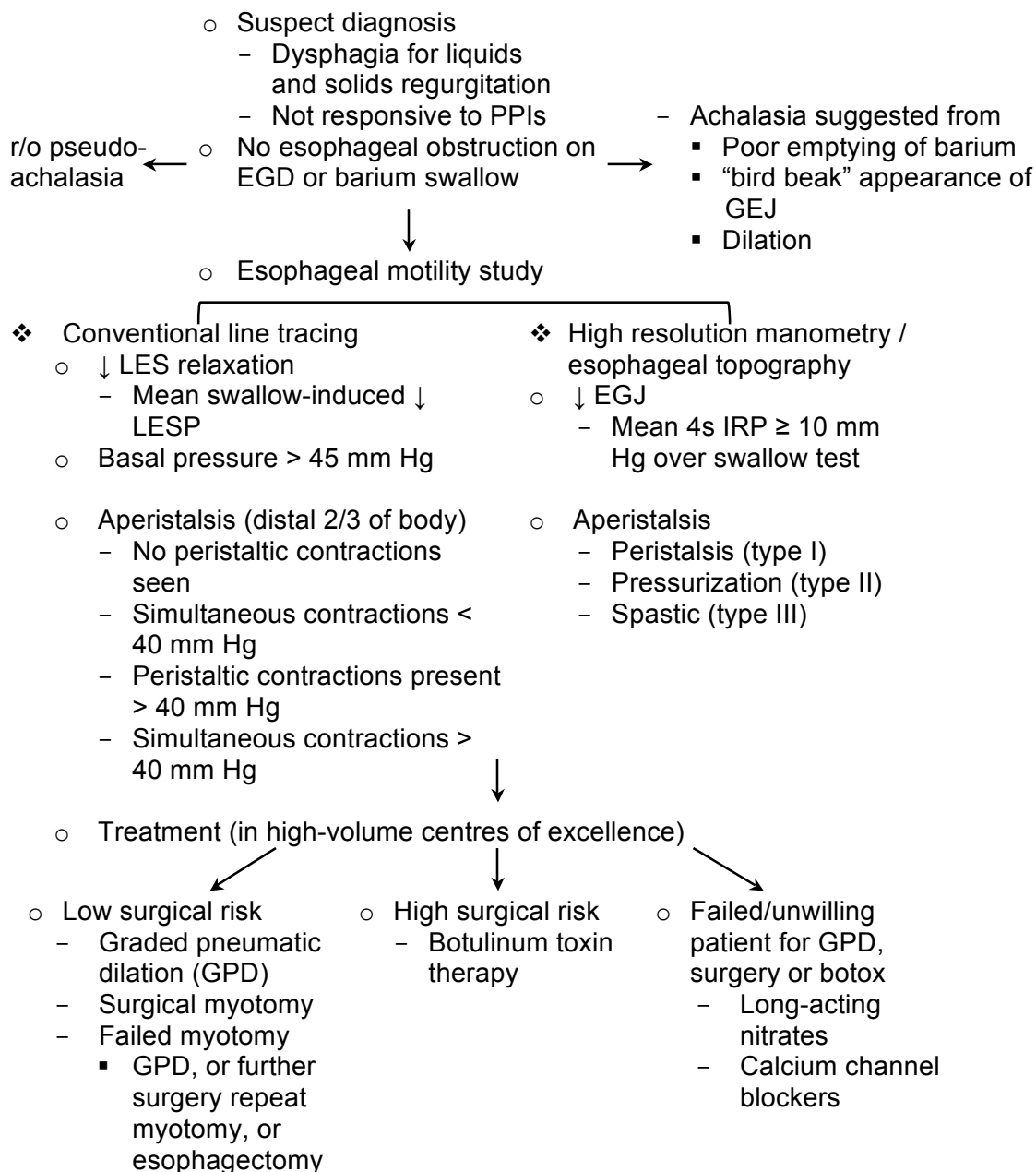
For details on food allergy testing in EoE, please see Aceves SS, et al. Clin Gastroenterol Hepatol 2014; 1216-1223.



ACHALASIA: ACG GUIDELINES

Abbreviations: ACG, American College of Gastroenterology

Vaezi MF, et al. Am J Gastroenterol 2013; 108: 1238-1249.



Abbreviations: EGJ, esophagogastric junction; GPD, graded pneumatic dilation; IRP, integrated relaxation pressure; LES, lower esophageal sphincter; LESP, lower esophageal sphincter pressure

Removal of Foreign Bodies

Non-cardiac (esophageal) Chest Pain (NCCP): please see the Expert Review (Coss-Adame E, et al. Clin Gastroenterol Hepatol 2014; 12: 1224-1245)



ESOPHAGEAL CANCER: NOGCA GUIDELINES

Abbreviations: NOGCA, National Oesophago-Gastric Cancer Audit

Allum WH, et al. Gut 2011; 60: 1449-1472.

- Prevention
 - Please see ACG guidelines for Barrett esophagus
- Diagnosis
 - Please see ACG guidelines for GERD
- Pathology and staging
 - Multidisciplinary team
 - Diagnostic imaging: CT chest, abdomen, pelvis; EUS; PET-CT
- Treatment
 - Choices depend upon
 - Patient preference and comorbidities
 - Tumour stage
 - Endoscopic
 - EMR / ESR, depending upon stage of mucosal / submucal lesion
 - Surgery
 - Prophylaxis
 - Antibiotics, antithrombotics
 - Procedure
 - No one procedure proven to be superior for resection
 - Operative experience ≥ 20 esophageal / gastric cancer resections per year
 - Squamous cell cancer
 - Localized to
 - Proximal 1/3 esophagus
 - Middle or distal 1/3
 - Chemoradiation +/- surgery
 - Adenocarcinoma
 - Preoperative chemoradiation, or chemotherapy (cisplatin, 5-fluorouracil [5-FU])
 - Junctional adenocarcinoma, type II/III
- Palliation
 - Symptom relief
 - Radiotherapy
 - External beam
 - Brachytherapy
 - Chemotherapy (combination)
 - Trastuzumab, cisplatin
 - Fluoropyrimidine
 - GEJ adenocarcinoma
 - Obstruction relief
 - Self-expanding stent
 - Firm stenotic tumour
 - Covered expandable metal stent
 - Perforation after dilation of malignant stricture
 - Malignant tracheo-esophageal fistula
 - Tumour
 - > 2 cm from cricopharyngeus
 - Patient
 - Poor prognosis
 - Rapid relief
 - Laser +/- brachytherapy or external beam radiotherapy
 - Exophytic tumours
 - Overgrowth at ends of stent
 - Argon plasma coagulation (APC)
 - Stent overgrowth
 - $\downarrow$ bleeding from inoperable tumour

Abbreviations: EMR, endoscopic mucosal resection; ESR, endoscopic submucosal; EUS, endoscopic ultrasound; GEJ, gastroesophageal junction



STOMACH

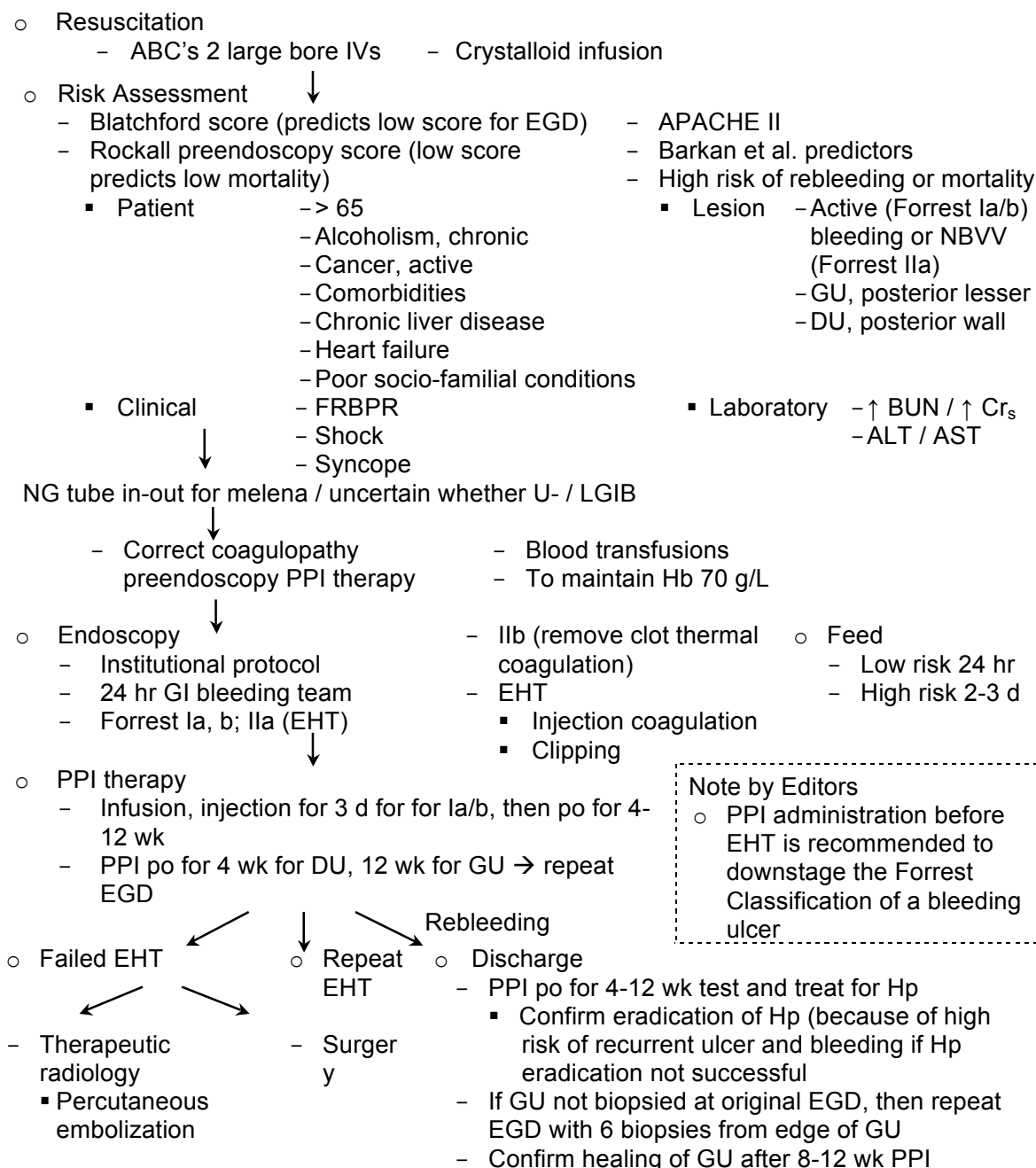


NON-VARICEAL UPPER GASTROINTESTINAL BLEEDING (NVUGIB): ICUGBCG GUIDELINES

Abbreviation: ICUGBCG, International Consensus Upper Gastrointestinal Bleeding Conference Group; NICE, National Institute of Health and Care Excellence

ICUGBCG. Barkan AN, et al. Ann Intern Med 2010; 152: 101-113; NICE: Dworzynski K, et al. BMJ. 2012; 344: e3412.

Please also see Hayes SM, et al. Can J Gastroenterol 2010; 24: 289-296.



Note by Editors

- PPI administration before EHT is recommended to downstage the Forrest Classification of a bleeding ulcer

Abbreviations: ALT / AST, aminotransferases; BUN, blood urea nitrogen; ASA, acetylsalicylic acid ("aspirin"); COX2, cyclooxygenase-2; Cr_s, serum creatinine; DU, duodenal ulcer; EGD, esophago-gastroduodenoscopy; EHT, endoscopic hemostatic therapy; FRBPR, fresh red blood per rectum; GU, gastric ulcer; Hb, hemoglobin concentration; Hp, *Helicobacter pylori* infection; LGIB, lower gastrointestinal bleeding; NBVV, non-bleeding visible vessel; NG, nasogastric; PPI, proton pump inhibitor



DYSPEPSIA: ACG / CAG GUIDELINES

Abbreviations: ACG, American College of Gastroenterology; CAG, Canadian Association of Gastroenterology

Moayyedi PM, et al. Am J Gastroenterol 2017; 112: 988-1013.

➤ Definition

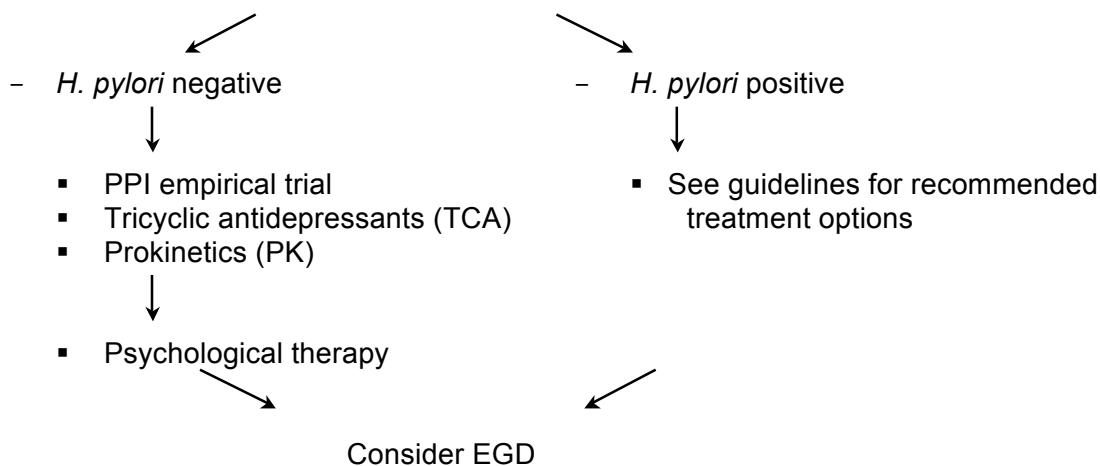
- Dyspepsia is "...predominant epigastric pain lasting at least 1 month"
- This can be associated with any other upper gastrointestinal symptoms such as epigastric fullness, nausea, vomiting, or heartburn, provided epigastric pain is the patient's primary concern.

➤ Demography

- Depending upon definition of dyspepsia, very common
 - ~30% of the population have ≥ 1 episodes in a yr

➤ Approach

- > 60 yr
 - EGD
 - EGD-negative
 - Treat for "functional dyspepsia"
 - EGD-positive
 - Treat underlying condition
- < 60 yr
 - EGD if
 - Childhood spent in a high risk gastric cancer country
 - Positive family history for gastric cancer
 - *H. pylori* test (urea breath test [UBT] or fecal antigen test (while off PPI / antibiotics))



➤ Useful RRs / NNTs

- Alarm symptoms are not an indication for EGD if patient < 60 yr
 - Individual alarm symptoms such as dysphagia, anemia or ↓ weight have low (~66%) sensitivities and specificities
 - Positive likelihood ratio of 2.74 (95% CI, 1.47 - 5.24)
 - Because risk of gastric cancer is low in USA / Canada, the risk of gastric cancer in a patient with an alarm symptoms is < 1%
- < 60, test and treat for *H. pylori* positive
- Undiagnosed dyspepsia
 - RR of remaining dyspeptic, 0.81 (95% CI, 0.70 - 0.94)
 - NNT, 7 (95% CI, 5-14)
- Dyspepsia, EGD performed and normal (functional)
 - RR of remaining dyspeptic, 0.91 (95% CI, 0.88 - 0.94)
 - NNT, 12.5
- < 60, no response to *H. pylori* eradication or empirical trial of PPI
 - TCAs reduced dyspeptic symptoms in 26% (RR, 0.74; 95% CI 0.61 - 0.91)
 - Note:
 - No benefit of selective serotonin reuptake inhibitors (SSRIs)
- Functional dyspepsia, no benefit of PPI, *H. pylori* eradication or TCAs → prokinetics
 - RR of remaining dyspeptic 0.92 (95% CI, 0.88 - 0.97)
 - NNT, 12.5 (95% CI, 8 - 25)
- No benefit of doubling dose of PPI (od → bid)
- No benefit of complementary or alternative medicines
- 4-hr solid phase gastric-emptying scan not performed routinely

Abbreviations: CI, confidence interval; EGD, esophagogastroduodenoscopy; NNT, number needed to treat; RR, relative risk

"When we are no longer able to change a situation,
we are challenged to change ourselves."

Viktor Frankl



Role of Upper Gastrointestinal Biopsy to Evaluate Dyspepsia in the Adult Patient in the Absence of Visible Mucosal Lesions: AGA Guidelines

Abbreviations: AGA, American Gastroenterology Association

Yang Y-X, et al. Gastroenterology 2015; 149: 1082-1087.

Note: This applies only to a “Western” population

➤ Summary of Statements

Anatomic Location	Statement
○ Esophagus	– In all patients (immunocompetent / compromised) undergoing EGD for dyspepsia as the sole indication – No routine biopsies of the normal appearing esophagus or GE junction regardless of immune status
○ Stomach	– Take biopsies of the normal-appearing gastric body and antrum for the detection of Hp infection if the Hp infection status is unknown. – Follow the 5-biopsy Sydney System with all specimens placed in the same jar. – 5 gastric biopsies for <i>H. pylori</i> (antrum X2, body X2) – Do not obtain automated special staining of the specimens.
○ Duodenum	– Do not obtain routine biopsies of the normal-appearing duodenum to detect celiac disease. – Obtain routine biopsies of the normal-appearing duodenum for the detection of GVHD in ▪ Post-allogeneic tissue transplantation patients and ▪ For opportunistic infections – Small bowel (duodenum) ▪ Only if immunocompromised (≥ 2 biopsies for GVHD) – Do not perform routine special staining of the specimens

Aide de memoire

- Dyspepsia, EGD and biopsy from abnormal appearing mucosa as appropriate (Different AGA guideline)

Abbreviations: EGD, esophagogastroduodenoscopy; GVHD, graft-versus-host disease



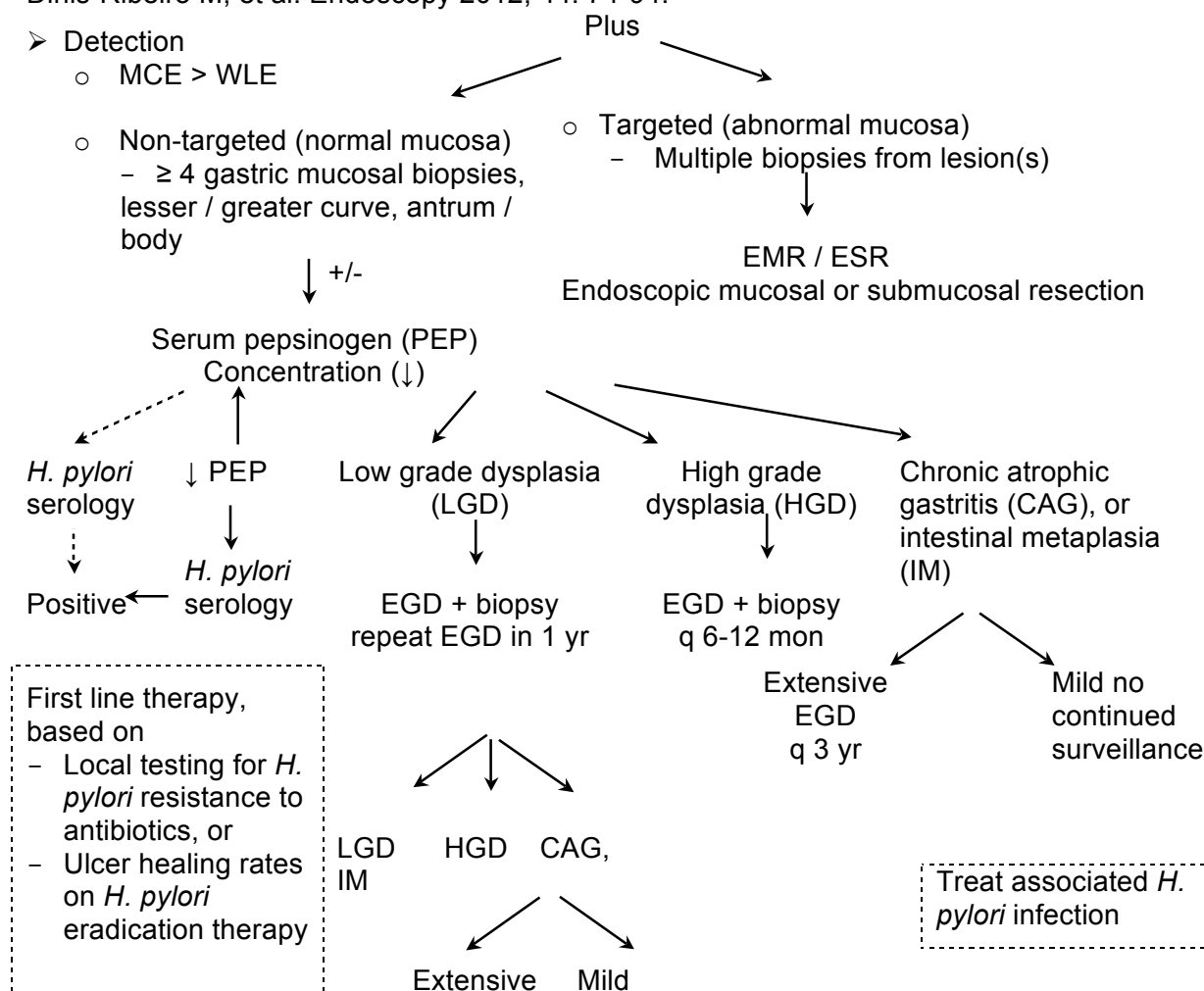
PREMALIGNANT GASTRIC LESIONS: ATROPHIC GASTRITIS (AG) AND GASTRIC INTESTINAL METAPLASIA (IM): HIGH RISK LESIONS FOR GASTRIC ADENOCARCINOMA: ESGE / EHSG / ESP GUIDELINES

Abbreviations: ESGE, European Society of Gastrointestinal Endoscopy; EHSG, European Helicobacter Study Group; ESP, European Society of Pathology

Dinis-Ribeiro M, et al. Endoscopy 2012; 44: 74-94.

➤ Detection

- MCE > WLE
- Non-targeted (normal mucosa)
 - ≥ 4 gastric mucosal biopsies, lesser / greater curve, antrum / body
- Targeted (abnormal mucosa)
 - Multiple biopsies from lesion(s)



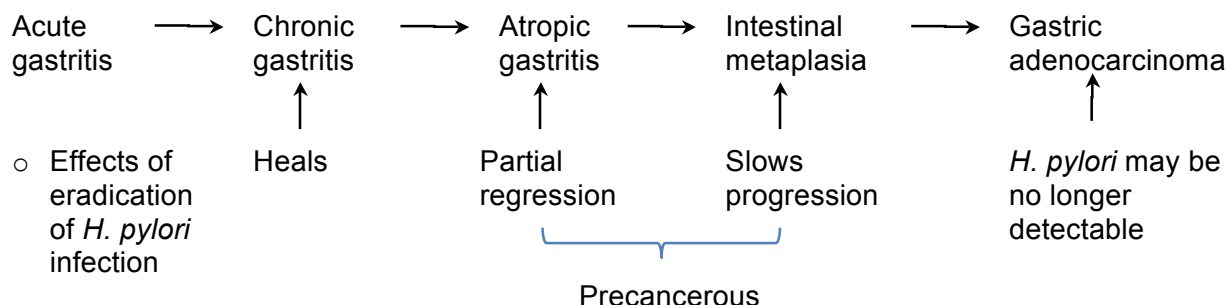
Abbreviations: CAG, chronic atrophic gastritis; EGD, esophagogastroduodenoscopy; *H. pylori*, *Helicobacter pylori*; HGD, high grade dysplasia; IM, Intestinal metaplasia; LGD, low grade dysplasia; PEP, serum pepsinogen concentration

Category	Recommendation
➤ Diagnosis	○ Conventional with light endoscopy cannot accurately differentiate and diagnose pre-neoplastic conditions. ○ For assessment of premalignant gastric lesions, diagnostic upper gastrointestinal endoscopy should include gastric biopsy sampling from antrum and corpus. ○ Systems for histopathologic staging may be useful for categorization of risk of progression to gastric cancer



Category	Recommendation
➤ Surveillance	○ Patients with extensive atrophy and / or intestinal metaplasia should receive surveillance with an interval of 3 yr. ○ Patients with low-grade dysplasia in the absence of endoscopically defined lesions should receive follow-up within 1 yr after diagnosis. ○ Patients with high-grade dysplasia in the absence of endoscopically defined lesions should undergo immediate endoscopic reassessment with endoscopic biopsy sampling and surveillance at 6 to 12 mon intervals. ○ Patients with endoscopically visible high-grade dysplasia or cancer should undergo staging and adequate management.
➤ Treatment	○ <i>H. pylori</i> eradication is recommended and heals non-atrophic gastritis but does not appear to reverse intestinal metaplasia.

- Give the role of treating and *H. pylori* infection on the prevention of gastric cancer.



Abbreviations: AG, atrophic gastritis; EDL, endoscopically defined lesion; EGD, esophagogastroduodenoscopy; EMR, endoscopic mucosal resection; HGD, high grade dysplasia; IM, intestinal metaplasia; LGD, low grade dysplasia

❖ Background

- Conventional white light endoscopy cannot accurately differentiate and diagnose pre-neoplastic gastric conditions.
- For assessment of premalignant gastric lesions, diagnostic upper gastrointestinal endoscopy should include gastric biopsy sampling from antrum and corpus.
- Systems for histopathologic staging may be useful for categorization of risk of progression to gastric cancer.
- Gastric carcinogenesis
 - Patients with chronic atrophic gastritis (AG) or intestinal metaplasia (IM) should be considered to be at higher risk for gastric adenocarcinoma
 - High-grade dysplasia and invasive carcinoma should be regarded as the outcomes to be prevented when patients with chronic atrophic gastritis or intestinal metaplasia are managed.



- Patients with endoscopically visible high grade dysplasia or carcinoma should undergo staging and adequate management
- Endoscopy
 - Conventional white light endoscopy cannot accurately differentiate and diagnose pre-neoplastic gastric conditions
 - Magnification chromoendoscopy and narrow band imaging (NBI), with or without magnification, improve the diagnosis of gastric preneoplastic conditions / lesions compared to white light endoscopy (standard, not high definition)
 - Within this content, diagnostic upper gastrointestinal endoscopy should include gastric biopsies sampling
- Biopsy sampling
 - AG / IM often unevenly distributed throughout the stomach
 - For adequate staging and grading of gastric precancerous conditions, at least four non-targeted biopsies of two topographic sites (the lesser and greater curvature, from both the antrum and the corpus) should be taken and clearly labeled in separate vials
 - Additional target biopsies of lesions should be taken
 - Systems for histopathological staging (e.g., operative link for gastritis assessment [OLGA] and operative link for gastric intestinal metaplasia [OLGIM] assessment) may be useful for categorization of risk of progression to gastric cancer.
 - Note (now in guidelines):
 - Updated Sydney classification underestimates AG / IM detection
 - 97% in 100% Ca
 - Antrum x 2, 3 cm from from pylorus (30%)
 - Incisura (40%)
 - Body g/L curative (30%)
- Non-invasive assessment
 - ↓ serum pepsinogen levels can predict extensive atrophic gastritis
 - In patients with low pepsinogen test levels, *Helicobacter pylori* serology may be useful for further detection of high risk individuals (evidence level 2++ recommendation grade C)
- Additional diagnostic factors
 - Intramucosal involvement
 - Family history of gastric cancer should be taken into account in the follow-up of precancerous conditions (evidence level 2++, recommendation grade B)
 - No clinical recommendations can be made for targeted management based on age, gender, *Helicobacter pylori* virulence factors, host genetic variations
- ❖ Surveillance
 - Dysplasia
 - Patients with low grade dysplasia in the absence of an endoscopically defined lesion should receive follow-up within 1 yr after diagnosis
 - In the presence of an endoscopically defined lesion, endoscopy resection should be considered, to obtain a more accurate histological diagnosis.
 - Patients with low-grade dysplasia in the absence of endoscopically defined lesion should receive follow-up within 1 yr after diagnosis.



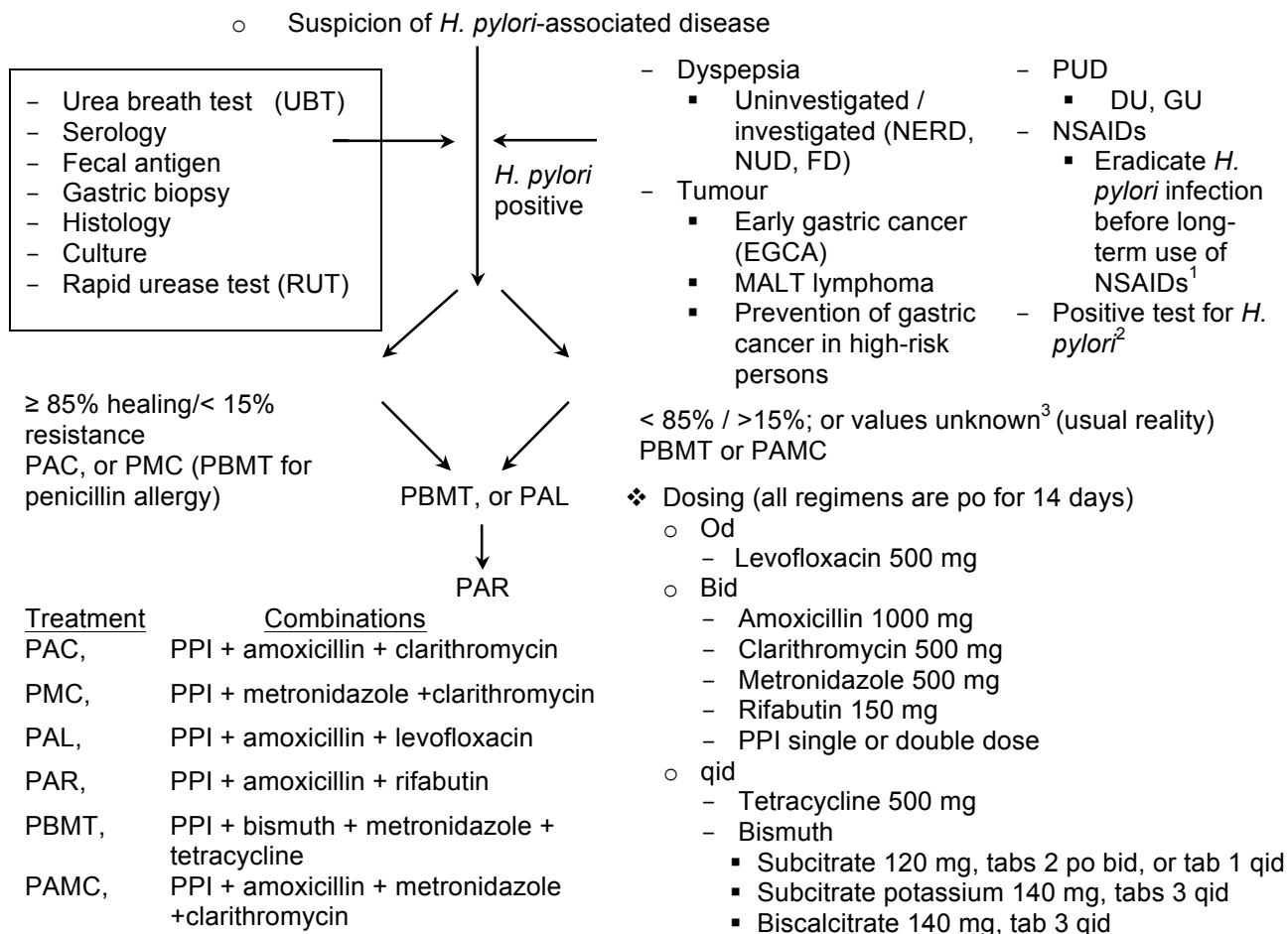
- Patients with high-grade dysplasia in the absence of endoscopically defined lesions should undergo immediate endoscopic reassessment with endoscopic biopsy sampling and surveillance at 6- to 12- mon intervals.
 - For patients with high-grade dysplasia in the absence of endoscopically defined lesions; immediate endoscopic reassessment with extensive biopsy sampling and surveillance at 6 month to 1 yr intervals.
- Atrophy or intestinal metaplasia (EGD)
 - Endoscopic surveillance should be offered to patients with extensive AG +/- IM in the antrum and corpus
 - Patients with extensive atrophy and / or intestinal metaplasia should receive surveillance with an interval of 3 yr.
- ❖ Eradication of *Helicobacter pylori*
 - *Helicobacter pylori* eradication
 - Heals non-atrophic chronic gastritis
 - May lead to partial regression of atrophic gastritis
 - Not in guidelines: consider proving (prove Hp eradication)
 - Does not reverse intestinal metaplasia but it may slow progression to neoplasia, and therefore it is recommended (evidence level 1+, recommendation grade B)
 - *H. pylori* eradication is recommended for patients with previous neoplasia after endoscopic or surgical therapy.
 - *H. pylori* eradication is recommended and heals non-atrophic gastritis but does not appear to reverse intestinal metaplasia.
- ❖ Additional measures
 - Currently, the use of cyclooxygenase-2 (COX-2) inhibitors cannot be supported as an approach to decrease the risk of progression of gastric precancerous lesions.
 - The use of dietary supplementation with antioxidants (ascorbic acid and betacarotene) cannot be supported as a therapy to reduce the prevalence of atrophy or intestinal metaplasia.
- ❖ Cost-effectiveness
 - After endoscopic resection of early gastric cancer (EGC), *Helicobacter pylori* eradication is cost-effective
 - Currently available evidence does not allow an accurate estimation of the cost-effectiveness of surveillance for premalignant gastric conditions worldwide.



HELICOBACTER PYLORI (*H. PYLORI*) INFECTION IN ADULTS: CAG / CHSG / TORONTO GUIDELINES

Abbreviations: CAG, Canadian Association of Gastroenterology; CHSG, Canadian Helicobacter Study Group

Fallone CA, et al. Gastroenterology 2016; 151: 51-69.



➤ Useful background – Approximate antibiotic resistant rates for *H. pylori* eradication

○ Amoxicillin	5%	○ Clarithromycin	20%
○ Metronidazole 1°	30%	2°	65%

¹ Although this recommendation is not in the CAG / Toronto guidelines, the eradication of *H. pylori*, is recommended by the Canadian Rheumatology Society.

² Although this recommendation is not in CAG / Toronto guidelines, but for medicolegal reasons it is necessary to treat anyone who has been tested and is positive.

² While not in the Toronto guidelines, in order to achieve the arbitrary threshold of *H. pylori* eradication rates of ≥ 90%, and because the local rates of *H. pylori* eradication or are usually unknown, the best treatment option is to assume the worse and use the treatment route.

⁴ Metronidazole 500 mg bid except for bismuth-containing combinations given qid.

Abbreviations: DU, duodenal ulcer; EGCA, early gastric cancer; GU, gastric ulcer; MALT, mucosal-associated lymphoid tissues; RUT, rapid urease test; UBT, urea breath test; 1°, primary; 2°, secondary



Treatment of *Helicobacter pylori* Infection: ACG Guidelines

Abbreviations: ACG, American College of Gastroenterology

Chey WD, et al. Am J Gastroenterol 2017; 112: 212-238.

➤ Testing

- Present or past peptic ulcer disease (including complicated PUD)
- Dyspepsia age < 60 yr, even without alarm symptoms
- MALT lymphoma
- Early gastric cancer (EGC), endoscopically resected
- Chronic intake of NSAIDs, ASA
- Unexplained iron deficiency anemia
- Idiopathic thrombocytopenia purpura (ITP)

↓

- The indication for treating *H. pylori* infection is a positive test

➤ Treatment

- First line
 - PCA or PCM for 14 d
 - Clarithromycin resistance < 15%
 - No previous exposure to "C" (macrolides)
 - PCAN
 - PBTN for 10-14 d
 - Previous macrolide exposure
 - Allergy to penicillin (A)
 - PA for 14 d
 - PA for 5-7 d, then
 - PCN for 5-7 d
 - PFN for 5-7 d
 - PCAN for 5-7 d

First line use of

C → PBTN or PLA

PBTN → PCA, PCM, PCAN, PLA

- Second line (avoid antibiotics that have been used for first line therapy, e.g., A, C, N, T)
 - PLA for 10-14 d
 - RAR for 10 d

Abbreviations: A, amoxicillin; B, bismuth; C, clarithromycin; F, fluoroquinolone; L, levofloxacin; M, metronidazole; N, nitroimidazole; P, proton pump inhibitor; PA, PPI + amoxicillin; PAC, PPI + clarithromycin + amoxicillin; PAR; PPI + amoxicillin + rifabutin; PBTN, PPI + bismuth + tetracycline + nitroimidazole; PCAN, PPI + clarithromycin + amoxicillin + nitroimidazole; PCM, PPI + clarithromycin + metronidazole; PCN, PPI + clarithromycin + nitroimidazole; PFN, PPI + fluoroquinolone + nitroimidazole; PLA, PPI + levofloxacin + amoxicillin; R, rifabutin; T, tetracycline



- Prove eradication (UBT, fecal antigen test, biopsy-based testing)
 - Withhold PPI for 1 – 2 wk
 - Retest 1 mon after course of *H. pylori* infection therapy
- Regression of MALT lymphoma with *H. pylori* eradication ~75%
- Recurrence
 - Macroscopic 3% in 24 mon
 - Microscopic 17% in 48 mon
- Note
 - Eradication of *H. pylori* may also be beneficial in gastric diffuse large B-cell lymphoma
- Eradication of *H. pylori* in early gastric cancer (EGC) → ↓ recurrence in ~50%
- In persons having a normal EGD for dyspepsia, biopsy for *H. pylori* and treat if positive (NNT to one patient with non-ulcer dyspepsia = 14)
- ASA 75 – 325 mg/d causes PUD (GU, DU) in ~10% of middle-to-older age patients
 - Eradication of ASA-associated DU (not GU) (OR 18.5; 95% CI 2.3 - 149.4)
 - Test for *H. pylori* infection when starting low-dose aspirin for prophylaxis
- NSAIDs associated ulcers ↓ 57% when *H. pylori* eradicated (OR = 0.43; 95% CI, 0.20 - 0.93)
 - Test for *H. pylori* infection when starting NSAIDs for long-term use in NSAID-naïve patients
 - Benefit of eradicating *H. pylori* infection in persons already on NSAIDs is less clear
- Eradicating *H. pylori* infection in TP Is beneficial
 - Response
 - Complete 43%
 - Partial (43% - 50%) 93%

"Goals in writing are dreams with
deadlines."

Brian Tracy



GASTRIC CANCER: NOGCA GUIDELINES

Abbreviations: NOGCA, National Oesophago-Gastric Cancer Audit

Allum WH, et al. Gut 2011; 60: 1449-1472.

- Prevention
 - Please see ACG guidelines for Barrett esophagus
- Diagnosis
 - Please see ACG guidelines for GERD
- Pathology and staging
 - Multidisciplinary team
 - Diagnostic imaging: CT chest, abdomen, pelvis; EUS; PET-CT
- Treatment
 - Choices depend upon
 - Patient preference and comorbidities
 - Tumour stage
 - Endoscopic
 - EMR / ESR, depending upon stage of mucosal / submucal lesion
 - Surgery
 - Prophylaxis
 - Antibiotics, antithrombotics
 - Procedure
 - No one procedure proven to be superior for resection
 - Operative experience ≥ 20 esophageal / gastric cancer resections per year
 - Squamous cell cancer
 - Localized to
 - Proximal 1/3 esophagus
 - Middle or distal 1/3
 - Chemoradiation +/- surgery
 - Adenocarcinoma
 - Preoperative chemoradiation, or chemotherapy (cisplatin, 5-fluorouracil [5-FU])
 - Junctional adenocarcinoma, type II/III
- Palliation
 - Symptom relief
 - Radiotherapy
 - External beam
 - Brachytherapy
 - Chemotherapy (combination)
 - Trastuzumab, cisplatin)
 - Fluoropyrimidine for HER₂+
 - GEJ adenocarcinoma
 - Obstruction relief
 - Self-expanding stent
 - Firm stenotic tumour
 - Covered expandable metal stent
 - Perforation after dilation of malignant stricture
 - Malignant tracheo-esophageal fistula
 - Tumour
 - > 2 cm from cricopharyngeus
 - Patient
 - Poor prognosis
 - Rapid relief
 - Laser +/- brachytherapy or external beam radiotherapy
 - Exophytic tumours
 - Overgrowth at ends of stent
 - Argon plasma coagulation (APC)
 - Stent overgrowth
 - $\downarrow$ bleeding from inoperable tumour

Abbreviations: EMR, endoscopic mucosal resection; ESR, endoscopic submucosal; EUS, endoscopic ultrasound; GEJ, gastroesophageal junction





SMALL BOWEL



CELIAC DISEASE

Diagnosis and Management of Celiac Disease: ACG / WGO Guidelines

Abbreviations: ACG, American College of Gastroenterology; WGO, World Gastroenterology Organization

Bai JC, et al. J Clin Gastro 2013; 47: 121-126; Rubio-Tapia A, et al. Am J Gastroenterol. 2013; 108(5): 656-676.

- When to suspect
 - Intestinal
 - Symptoms, signs, nutrient deficiency, or ↑ aminotransferase
 - Extraintestinal
 - Persons with celiac-associated disorders such as hypothyroidism, type I diabetes mellitus (DM-T1), or person with dermatitis herpetiformis (DH)
 - Family history
 - First degree relative with / without symptoms
- Diagnosis
 - Serology
 - Perform serological test for celiac disease (CD) in persons with
 - Compatible symptoms
 - Deficiencies (such as unexplained iron deficiency)
 - Disease associations (with 2x ↑ risk of CD vs general population, such as type I diabetes mellitus) and
 - Possibly in first degree family members with CD
 - In children > 2 yr and adults on a gluten-containing diet
 - No IgA deficiency
 - IgA anti-tissue transglutaminase
 - Possible / actual IgA deficiency
 - IgG TTG, IgG-deamidated gliadin peptides (DGP)
 - Duodenal mucosal biopsies bulb 2, distal duodenum ≥ 4
 - Compatible with CD
 - Dietitian-assisted gluten-free diet (GFD) for life
 - Micronutrient testing and replacement
 - Periodic follow-up with dietitian and physician for history, serology and normalization of previously abnormal deficiency
 - Biopsies
 - Not compatible / equivocal (e.g., GFD)
 - Mismatch between serology and histology
 - Repeat EGD + biopsies in 1-2 yr while on non-GFD
 - Refractory CD / diagnosis of challenged CD
 - Down syndrome
 - Non-responsive to GFD
 - HLA-DQ2 / DQ8 (positive) → Formal gluten challenge
 - Non-response
 - NRCD / refractory CD (RCD) type I/II
 - HLA DQ2 / DQ8 testing repeat EGD plus duodenal biopsies
 - Histochemistry of IELs
 - Flow cytometry
 - ↑ CD3+ cells
 - ↓ CD8+
 - Molecular analysis
 - Clonal T-cell receptor gene rearrangement



- Refractory CD
 - VCE
 - Medication
 - Aggressive nutritional support
 - Small bowel biopsy (SBBx)
 - Site
 - Duodenum
 - Bulb 2
 - Distal 4
 - Minimum of 6 biopsy
 - High- and low-power changes may be compatibly supporting the diagnosis (change are not pathognomonic)
 - Capsule endoscopy (CE)
 - Endoscopy-based SBBx not possible / declined
 - Examination of small bowel for complication of CD such as relapsing / refractory CD, ileojejunitis, lymphoma
 - HLA DQ2 / DQ8 antigen testing
 - tTG negative and SBBx shows equivocal / discrepant changes of CD
 - Persistent / recurrent symptoms despite adherence to a gluten-free diet (GFD)
 - Patients biopsied while on a GFD, with no initial SBBx before the GFD
 - Down syndrome (high pretest probability of CD)
 - Gluten challenge (rarely performed)
 - 10 g gluten (2 slice of bread) per day for 2-8 wk; then repeat CD serology +/- SBBx
- ↓
- Treatment
- CD diagnosed
 - Non-celiac gluten sensitivity (NCGS)
 - Negative tTG and SBBx, but response to gluten-free diet (HLA DQ2 / DQ8 must be negative to diagnose NCGS)
 - Test and treat for nutrient deficiencies
 - Bone mineral density testing (DEXA scan) when appropriate
 - Consultation with registered dietitian
 - Gluten-free diet lifelong
 - NCGS: HLA DQ2 or DQ8 negative, normal tTG serology and SBBx when on GFD
- ↓
- Persistent / recurrent symptoms despite GFD
- T cell surface markers to differentiate type I vs type II refractory CD
 - Aggressive nutritional therapy, including TPN as necessary
 - Consideration for immune suppression or hematopoietic bone marrow transplantation
- ↓
- Follow up
- Monitor growth and development in children
 - Clinical assessment for symptoms (residual or new)
 - Verification of continued normalization of abnormal laboratory values pre-GFD
 - DEXA SCAN (for bone mineral density), when patient is at risk for osteoporosis



➤ Histology Marsh and Carazza Classifications

Marsh Modified (Oberhuber)	Histological Criteria			Corazza
	↑ IEL *	Crypt Hyperplasia	Villous Atrophy	
Type 0	-	-	-	None
Type 1	↑	-	-	Grade A
Type 2	↑	✓	-	
Type 3a	↑	✓	Partial	Grade B1
Type 3b	↑	✓	Subtotal	
Type 3c	↑	✓	Total	Grade B2

* > 40 intraepithelial lymphocytes (IEL) per 100 enterocytes for Marsh modified (Oberhuber); > 25 intraepithelial lymphocyte per 100 enterocytes for Corazza

Note: These histological classifications do not correlate closely with the severity of clinical features

❖ Other Causes of Villous Atrophy in Duodenum

- Infection
 - Small-intestinal bacterial overgrowth (SIBO)
 - Whipple disease
 - Giardiasis
 - Intestinal tuberculosis
- Iatrogenic
 - Drug-associated enteropathy (e.g., olmesartan)
- Malnutrition
 - Infectious enteritis
- Infiltration
 - Intestinal lymphoma
- Immune
 - Autoimmune enteropathy
 - Hypogammaglobulinemic sprue
 - Collagenous sprue
 - Tropical sprue
 - Crohn disease
 - Eosinophilic enteritis
 - Graft-versus-host disease
 - Acquired immune deficiency syndrome enteropathy

Abbreviations: DGP, deamidated gliadin peptides; GFD, gluten-free diet; NRCD, non-responsive celiac disease; RCD, refractory celiac disease; VCE, video capsule endoscopy

Source: Rubio-Tapia A, et al. Am J Gastroenterol 2013; 108: 656–676; and Bai JC, et al. J Clin Gastroenterol 2013; 47: 121–126.

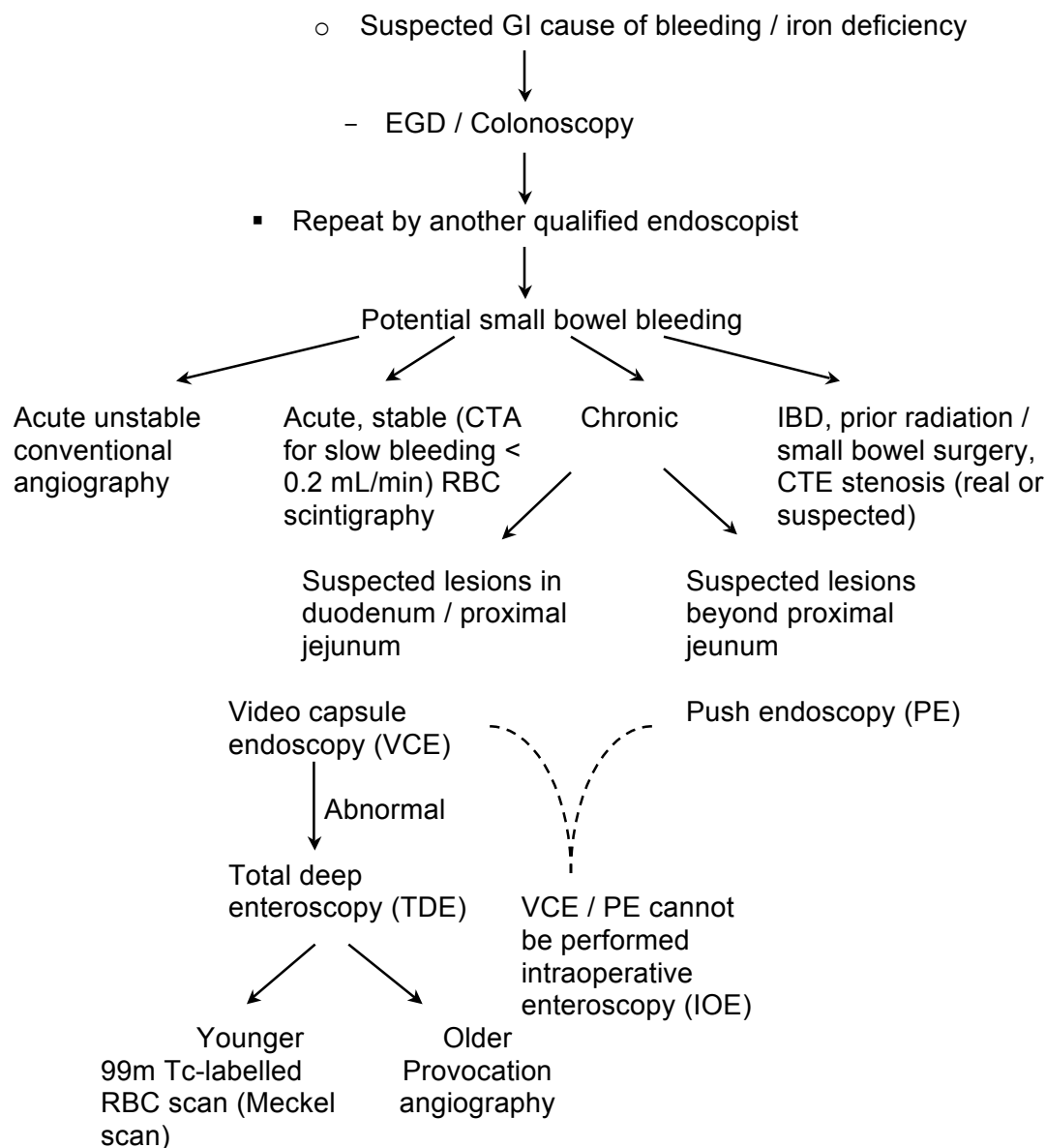


SMALL BOWEL BLEEDING

Diagnosis and Management of Small Bowel Bleeding: ACG Guideline

Abbreviations: ACG, American College of Gastroenterology

Gerson LB, et al. Am J Gastroenterol 2015; 110: 1265-87.



Abbreviations: CTA, CT angiography; CTE, CT enteroscopy; EGD, esophagogastroduodenoscopy; IBD, inflammatory bowel disease; IOE, intraoperative enteroscopy; PRBC, packed red blood cells; RBC, red blood cell; TDE, total deep enteroscopy; VCE, video capsule endoscopy



BENIGN CHRONIC INTESTINAL FAILURE (CIF) IN ADULTS: ESPEN GUIDELINES

Abbreviation: ESPEN, European Society for Clinical Nutrition and Metabolism

Pironi L, et al., Clin Nutrition 2016; 35: 247-307.

- Definition of terms
 - Intestinal failure
 - Gut function reduced below the minimal necessary for the absorption of macronutrients and / or water and electrolytes, such that intravenous (IV) supplementation is required to maintain health and / or growth.
 - Intestinal insufficiency/deficiency
 - Gut function reduced but not to the extent that IV supplementation is required
- Demography
 - CIF ~ 2/10⁵
- Classification
 - Give the classifications of the intestinal failure based upon functional, pathophysiological, and clinical factors.
 - Functional
 - Type I
 - Acute, short term, self-limiting condition
 - Type II
 - Prolonged acute, metabolically unstable, IV nutrition needed over weeks or a few months
 - Type III
 - Chronic, metabolically stable, IV nutrition needed over many months or years
 - Pathophysiological
 - Exterior small bowel mucosal disease (5%)
 - Bowel
 - Short (75%)
 - Fistula (2%)
 - Obstruction (mechanical occlusion)
 - Dysmotility (disorder of propulsion, no mechanical occlusion; aka “chronic intestinal pseudo-obstruction”, 18%)
 - Clinical (requirements for IV energy and volume)
 - Volume (mL) of IV supplementation, calculated as
 - The daily mean of the total volume infused per wk, or
 - Volume of infusion per day x the number of infusions per wk/7
 - IV energy supplementation, calculated as
 - The daily mean of the total energy infused per wk, or
 - Energy per day of infusion x number of infusions per wk/7



Complications

❖ Liver Disease

- Definition
 - No accepted clinical, laboratory or histopathological definition
- Demography
 - Incidence / prevalence vary widely depending upon definition used to diagnosis
- Treatment
 - Liver
 - Prevent / treat associated infection / sepsis
 - Continue
 - PO / PN nutrition
 - PN
 - Cycle
 - Do not give excess
 - Lipids
 - Soybean-oil lipids < 1 g/kg per day
 - ↓ total fatty acids
 - ↓ ratio of ω -6 / ω -3 fatty acids
 - Biliary tree
 - Use oral intake whenever possible
 - Biliary complications
 - Gallbladder stones (cholelithiasis) → cholecystectomy
 - Bile duct stones (choledocholithiasis) ERCP plus sphincterotomy, stone extraction +/- stent

❖ Kidney Disease

- Demography
 - Creatinine clearance ↓~3.5% per year
- Prevention
 - Avoid nephrotoxic drugs
 - Repeated episodes of dehydration
- Treatment
 - Monitor / treat
 - ↑ serum creatinine (Cr_s)
 - Infections
 - Dehydration
 - Diet
 - ↓ oxalate, ↓ fat, ↑ calcium (↓ risk of oxalate stones)
 - Citrate supplements
 - Correct metabolic acidosis
 - ↓ risk of uric stones



❖ **Gallbladder: Cholelithiasis**

➤ Demography

- Incidence
 - 1 yr, 21%
 - 2 yr, 39%

➤ Causes / associations

- ↓ / no oral intake
 - Stasis of gallbladder
- Short bowel < 18 cm
- Ileocecal junction resected
- Duration of PN
- Underlying Crohn disease
- Use of narcotics, anticholinergics

❖ **Bone: Metabolic Bone Disease**

➤ Causes / associations

- Drugs
 - Use of corticosteroids
 - Aluminium (e.g., antacid, PN solution)
- Vitamin D
 - ↑ sensitivity to vitamin D → ↓ PTH secretion
- Hypercalciuria
 - From ↑ Ca²⁺ excretion

➤ Diagnosis

- Routine monitoring HPN-treated persons with
 - Blood work
 - Ca_s, PO₄, vitamin D, PTH
 - DEXA SCAN for bone mineral density
- Risk factors
 - E.g., early treatment of infection / inflammation
 - Supplements of Ca, PO_{4s}, vitamin D, as indicated

Abbreviations: Ca_s, serum calcium concentration; PO_{4s}, serum phosphate concentration

➤ Treatment

- Prevention
 - Yearly DEXA SCAN of
 - Spine
 - Femoral neck or arm
- IV bisphosphonates



SHORT BOWEL SYNDROME (SBS)

- Note
 - A shortened bowel (< 200 cm) is one of the pathological classifications of intestinal failure

	Surgery	Colon in Continuity
○ Types	- End jejunostomy - Jejunocolic - Jejunoleal	▪ None ▪ Some (no ICV) ▪ All (ICV)

Abbreviation: ICV, ileocecal valve

➤ Prognosis

- Weaning of HPN (reversibility)
 - Partial
 - ~ 50%, especially if some or all of the colon is in continuity
 - Complete < 10% after 2 yr
- Mortality
 - 20% in 5 yr

➤ Treatment

- Objectives of care
 - The purpose of monitoring patient on HPN is to “secure and improve” quality of life
 - Recommended frequency q 3 mon
 - Multidisciplinary teams including registered dietitians and specialist nurses, and larger experienced teams, have a superior outcome

- Identify “key interventions” to maintain quality of care
 - Structure
 - Administrative standards
 - Process
 - How care is provided
 - Outcome
 - Expected/desired benefits for patients

- HPN program
 - Appropriate equipment
 - Multidisciplinary team
 - Regular audit
 - Prevention of HPN-associated complications
 - Maximize patient's quality of life
- Patient
 - Confirmed diagnosis of chronic intestinal failure
 - Metabolically stable
 - Sufficient support in an adequate home environment
 - Regular contact with HPN multidisciplinary team
 - Involvement with members of patient-help group



- Parenteral nutrition formulation
 - Correct deficiencies
 - Glycemic control
 - Blood Sugar Concentration Targets

	mg/dL	mmol/L
- Fasting	< 140	< 7
- Pre-infusion	100-140	4-7
- During HPN	140-180	7-10
 - HbA1C targets

	0.5-6.5%	48-58 mmol/mol
 - Insulin dosing for every 20 g of glucose in parenteral nutrition (PN)
 - IU insulin
 - Short activity 2/3
 - HPN 1/3
 - Maintain protein and energy requirements based on
 - Optimal blood glucose concentration
 - Essential fatty acids (EFA)
 - Soybean-based lipid emulsion 1 g/kg per wk (no higher)
- Prevention of deficiency of essential fatty acids (EFA; linoleic and α -linolenic acids)
- Soybean oil lipid emulsion 1g/kg per week
- Target T:T (triene / tetraene) ratio < 0.2

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- Give the name of the ratio of eicosatrienoic/arachidonic
 - T:T ratio, aka the Holman Index
- Give the clinical findings of linoleic acid/essential fatty acid deficiency occurring in a patient who is on HPN.
 - Skin
 - Thin, dry, scaling
 - Alopecia
 - Neurological and hematological changes
 - Regular monitoring and correction of laboratory blood abnormalities
 - Electrolytes, creatinine, acid-base status, vitamins, mineral, trace elements, urine volume

○ Composition of HPN Solutions	% of Total Calories	% of Non-protein Calories
- Carbohydrate	15-30%	30-50%
- Lipid		
- Protein	0.8-1 g/kg per day	



HPN Tip

Go on the higher side of the normal range for amino acids, since “amino acid [AA] solution provide 17% less protein substrate than the sum of their constituent amino acids” (lack of equivalence of daily AA for daily protein needs, i.e., ↑AA intake needed).

❖ Volume Requirement to Prevent Complications

- Give complications of acute / chronic volume depletion.
 - Dehydration
 - Electrolyte / acid base abnormalities
 - Renal failure
 - Renal calculi
 - Oxalate
 - Calcium
 - Water requirements (normal renal function)
 - 25-35 mL/kg per day
 - Urine output 0.8-1 L per day

Clinical Pearl

- The demonstration of postural tachycardia and hypotension (SBP > 20 mm Hg, DBP > 10 mm Hg is suggestive of volume depletion, as also is ↓ UO, ↓ BW, ↓ JVP
- Laboratory changes include ↑.Hct, ↑.Cr_s/↑.BUN, ↑.Osm_u (> 450 mOsm/kg)

Abbreviations: BUN, blood urea nitrogen; BW, body weight; Cr_s, serum creatinine; DBP, diastolic blood pressure; Hct, hematocrit; JVP, jugular venous pressure; Osm, osmolarity of urine; SBP, systolic blood pressure; UO, urine output

- Note
 - The ideal water and electrolyte intakes per day are recommended below, but are not evidence-based and must be adjusted on an individual bases.

	Per day (mL; mmol)	mmol/kg per day
– Water	1500-2500	2.5-3.5
– Na ⁺ (sodium)	60-150	} 1.0-1.5
– K ⁺ (potassium)	40-100	
– Cl ⁻ (chloride)		
– PO ₄ ²⁻ (phosphate)	10-30	0.3-0.5
– Mg ²⁺ (magnesium)	4-12	} 0.1-0.15
– Ca ²⁺ (calcium)	2.5-7.5	



- Suggestion (not a Guideline Recommendation)
 - In the patient on HPN, perform annual measurements of vitamin A, D, E, B12 and folic acid.
 - Measurement of primary and secondary electrolytes, as well as INR (vitamin K) can also be justified.

Printed with permission: Pironi L, et al. Clin Nutrition 2016; 35: 247-307.

- In the context of the patient on HPN, give the common causes of abnormalities of the following electrolytes.
 - $\downarrow K_s^+$
 - Short bowel length
 - Hypomagnesemia ($\downarrow Mg_s^{2+}$)
 - Drugs
 - Furosemide
 - Amphotericin B
 - $\uparrow K_s^+$
 - Drugs
 - Aldosterone
 - Octreotide
 - Heparin
 - Hemolysis
 - PO_{4s}^{2-}
 - Drugs
 - Bisphosphonates
 - Insulin
 - Parenteral mutation
 - Refeeding syndrome

$\uparrow$ Loss of Secretions

- Hypochloremic metabolic alkalosis
 - Stomach (loss of H^+)
- Hyperchloremic metabolic acidosis (normal anion gap)
 - Upper small intestine (loss of HCO_3^-)

Abbreviations: K_s^+ , serum potassium; Mg_s^{2+} , serum magnesium; PO_{4s}^{2-} , serum phosphate

- Metabolic acidosis with $\uparrow$ anion gap
 - $\uparrow$ D-lactic acid (bacterial overgrowth)
 - L-lactic acid (thiamine deficiency or PN mixture with $\uparrow$ cysteine, cysteine, methionine)
- $\uparrow PO_{4s}^{2-}$
 - Renal failure
 - High dose vitamin D



- Daily doses of trace elements for parenteral nutrition

Trace Elements	Micromol	mg/mcg	
Zinc	38-61	2.5-4	} mg
Copper	4.7-9.6	0.3-0.5	
Iron	17.9	1	
Manganese	1.1-1.8	60-100	} mcg
Chromium	0.2-0.3	10-15	
Selenium	0.2-0.8	60-100	
Iodine	0.5-1.2	70-150	

Recommendations have been published in an ASPEN position paper (Vanek VW, et al. Nutr Clin Pract 2012; 27: 440-491) on the recommended daily doses of trace elements for parenteral nutrition.

- Strategies to optimize small intestinal adaptation / habitation
- Balanced diet, eaten in ↑ amounts (hyperphagia), achieved with dietary counselling by a registered dietitian
- ↑ complex carbohydrates
- ↓ total fats (long-chain triglycerides)
- Consider use of medium-chain triglyceride
- Provide adequate fat-soluble vitamins as well as essential fatty acids
- Provide adequate fiber
- Exclusion of lactose only for symptoms of lactose
- Low amounts of IV supplement required (e.g., < 1000 mL/day), consider
 - Oral isotonic polymeric supplement
 - No restriction on table salt po
 - Adequate po intake of fluids
 - If necessary, use isotonic high sodium oral rehydration solutions
- High output jejunostomies
 - Normal NaCl intake
 - Isotonic fluids (avoid hypo- / hypertonic)
 - Loperamide (monitor biochemistry of stools / urine)
- Drugs
 - Where appropriate and possible, measure blood concentrations of drugs, the dose of which might need to be increased in proportion to its possible malabsorption.
- Consider if patient suitable to treat with teduglutide (GLP-2 analog) in consultation with expert intestinal failure and SBS.
- Consider pros and cons of treatment with growth hormone.
- Antibiotics if symptoms intolerance small intestinal bacterial growth (SIBO)



- Give the name of the conditionally essential amino acids, which do not need to be routinely added to HPN.
 - Cysteine, glutamine, taurine
- Give the importance of the colon being in place after an extensive small bowel resection.
 - Short bowel, no colon
 - ↑ intake (hyperphagia) of usual whole foods
 - Colon present
 - ↑ Carbohydrate (60%), ↓ lipids (20%), plus supplements of fat-soluble vitamins (A, D, E and K), as well as essential fatty acids (linoleic and linolenic)

To Look Impressive on Daily Rounds

- In the patient with SBS and a colon in place, the colon ferments carbohydrates, which are malabsorbed by the short bowel and spilled into the colon, forming short chain fatty acids (SCFAs).
 - The SCFAs are absorbed by the colon, and deliver about 1000 kcal per day of salvaged calories.
- Give the reason why some patients with SBS fed a high lipid / low carbohydrate diet may be switched to a low lipid plus MCT / high carbohydrate diet.
 - In SBS, long-chain fatty acids (LCFAs) may be malabsorbed by remaining small intestine.
 - The LCFAs spilled into the colon may cause adverse effects
 - Rapid transit
 - ↓ absorption of Na^+ / H_2O → diarrhea
 - ↑ binding of Ca^{2+} / Mg^{2+}
 - ↑ oxaluria (oxalate renal stones)
 - With ↑ carbohydrate (CHO) intake and the presence of a colon
 - CHO → SCFA → ↑ SCFA absorption → colonic salvage of ~ 1000 kcal/day
 - MCT can be absorbed without
 - Pancreatic digestion (lipase)
 - Solubilization (bile salts)
 - Export from enterocytes in lipoproteins across the basolateral membrane into lacteals (MCTs exit into portal circulation)

Clinical Gem

- Give the simple laboratory measurement which is a surrogate marker for the intestinal absorption of $\text{Na}^+/\text{H}_2\text{O}$ in the patient with SBS.
 - Measure urine volume (UV, < 800-900 mL/day and sodium urine (Na_u^+ < 35 mmol/day) from a 24-hr collection

Abbreviation: Na_u^+ , concentration of sodium in the urine



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- In the context of the patient with SBS and jejunostomy, give the meaning of a “secretor”.
 - Some patients with a jejunostomy may spill more $\text{Na}^+/\text{H}_2\text{O}$ into the stoma effluent than they ingest and absorb.
 - In these persons
 - $\uparrow$ oral intake $\rightarrow \uparrow$ stomal losses
 - The lack of a distal ileum and colon $\rightarrow \downarrow \text{Mg}^{2+}$ absorption $\rightarrow \text{Mg}^{2+}$ deficiency

To Look Impressive on Daily Rounds

The jejunal absorption of $\text{Na}^+/\text{H}_2\text{O}$ is greatly enhanced by adding rapidly absorbed glucose, which cotransports Na^+ secondarily and passively transports water with it.

- Give the ideal ratio of glucose to Na^+ for an oral rehydration solution (ORS).
 - A ratio of NaCl to glucose of 4-to-1 is the optimal ratio for ORS.
 - NaCl 120 mmol/L; glucose 30 mmol/L (2160 mg NaCl, 540 mg glucose)

Clinical Tidbit

- In a patient with SBS, fluids should be consumed with food, and not restricted with food intake at meals.
-
- Give the site of resection of the GI tract, which is most likely to be associated with the reduced concentration of serum Magnesium (Mg^{2+}), and give the reason why.
 - Magnesium is preferentially absorbed in the terminal ileum and colon
 - Resection of these sites is most likely to lead to hypomagnesemia ($\downarrow \text{Mg}^{2+}$)
 - Give the reason why the presence of the colon is important in the patient with a short bowel.
 - Nutrients not absorbed in short segments of small intestine spill into the colon
 - ↓
 - The colonic bacteria convert the effluent into short chain fatty acids (SCFA)
 - ↓
 - The SCFA are absorbed by the colon, and this represents the salvaging of 120 kcal/day



MCQ TIPS

- $\downarrow \text{Mg}^{2+} \rightarrow \downarrow \text{K}^+$ (hypomagnesemia may cause hypokalemia)
- Measurement of Mg_u^{2+} is superior to measuring Mg^{2+} to detect body depletion of Mg^{2+}
- Give which form of vitamin D should be measured.
 - It depends on the question causes for a disorder in calcium/vitamin D metabolism?
 - Is there a nutritional deficiency of vitamin D due to IF/SBS?
 - 1, 25 hydroxy vitamin D
 - Is there a renal cause for a disorder in calcium/vitamin D metabolism?
 - 1, 25 dihydroxy vitamin D
- In the patient with oxalate nephrolithiasis, give which water-soluble vitamin must not be taken in excess.
 - Vitamin C may be metabolized to oxalate, so excess amounts of vitamin C must not be taken in the patient with hyperoxaluria.

“All our dreams can come true – if we have the
courage to pursue them.”

Walt Disney



CENTRAL VENOUS CATHETER (CVC) COMPLICATIONS

- ≥ 2 thrombosis of
 - Internal jugular vein
 - Subclavian vein
 - Femoral vein
 - Infection
 - Systemic sepsis ≥ 2 episodes/yr (requiring hospitalization)
 - Fungemia, 1 episode
 - Acute respiratory distress syndrome (ARDS), 1 episode
 - Dehydration several episodes of severe dehydration despite HPN
 - Intra-abdominal desmoid tumour
 - High morbidity / low acceptance of HPN
- Types of CVC for long-term HPN
- Broviac, Hickman, Groshong
 - AV shunt versus CVC
 - $\uparrow$ clots
 - $\downarrow$ infection
 - No difference in rate of complications when using internal jugular, subclavian or femoral vein

Catheter-related Bloodstream Infections (CRBSIs)

- Definition
- CVC left in place
 - Blood cultures from catheter and from a peripheral vein $\rightarrow$ same organism, and no other source of infection
 - CVC removed
 - Positive culture of the catheter
 - Plus
 - $\downarrow$ temperature by 1°C in 1 day, or $\downarrow$ by 2°C in 2 days
 - $\downarrow$ WBC
 - Resolution of clinical symptoms / signs
 - Colonization of catheter

- Semi-quantitative > 15 cfu - Quantitative culture > 10^3 cfu	}	In absence of symptoms (usually bacterial)

Abbreviations: cfu, colony-forming units



- CRI
 - Local
 - Red, hot, sudden, painful site of catheter (usual fungal)
- Exit-site infection
 - Inflammation / pus within 2 cm of the catheter exit site
- Tunnel infection
 - Inflammation / pus > 2 cm of the catheter exit site
- Pocket infection
 - Inflammation / necrosis over the reservoir of the implantable port
- CRI
 - Origin of infection
 - Extra-luminal
 - Exit site of catheter
 - Tunnel tract
 - Endo-luminal
 - Hub of catheter
- Demography (CRBSI)
 - 0.14 - 1.1 episodes per catheter year
 - Accounts for 70% of hospitalizations of HPN patients
- Microbiology
 - Gram-positive
 - *Staphylococcus epidermids* ~50%
 - *S. aureus* ~10%
 - Gram-negative 16%
 - Fungi 3%
 - Polymicrobial 6%
- Laboratory
 - Suspect CRBSI when patient has non-specific symptoms, even without fever and when there are non-specific laboratory signs
 - ↑ c-reactive protein (CRP)
 - ↑ bilirubin
 - ↓ albumin
- Indications for removal of CVC
 - Give the indications for removal of CVC.
 - Abscess of port
 - Infection, tunnel
 - Septic shock



- Complicated CRBSI
 - Endocarditis
 - Infections
 - Metastatic
 - Fungal
 - Virulent bacteria

Clinical Tip

- There is no role to take routine aspirates and culture to attempt to treat early asymptomatic CRIs.

➤ Treatment

- Multidisciplinary HPN team
- Protocol
 - Hand-washing with 2% chlorhexidine
 - Patient
 - Medical team
 - Disinfect hub connector
 - Regular change of IV administration sets
 - Weekly change of catheter dressings
 - Do not perform CVC care after emptying ostomy
 - Disinfect hands after ostomy care
- Venous access
 - IJV / SV → R-sided SVC using ultrasound guidance
 - Single-lumen catheter
 - Tips of catheter at level of junction of RA / SVC
 - Catheter tunneled or implanted, with sufficient length of external catheter for patient to perform self-care
- CV infections
 - Simple infections
 - Antibiotics through CVC
 - Tunnel infection
 - Bacteremia with virulent bacteria / fungi
 - Port abscess
 - Complicated infections
 - Patient hemodynamically unstable

Abbreviations: IJV, internal jugular vein; RA, right atrium; SV, subclavian vein; SVC, superior vena cava

➤ Prognosis (CRIs)

- Site

- CRBSI	80%	}	Long-term mortality of HPN	→ Sepsis 30%
- Exit site	17%			→ CRIs 15%
- Tunnel	2%			



Public Safety

- Wash with alcohol, or with soap and water to ↓ H1N1 influenza on hands?
 - Soap and water is better
 - Alcohol is better than nothing

More on Antibiotic Prophylaxis

- Suggestion, but not a guideline, to use prophylactic antibiotics in HPN patients having dental work.
 - ↓ infection rate 50%
- Otherwise
 - Use ethanol therapy to ↓ CRBSI-related hospitalization (10 → 3 per 10³ catheter year)
 - Use taurolidine to
 - ↓ rate of infection (90%)
 - ↓ rate of occlusion

Catheter-related Occlusion / Thrombosis

- Demography
 - Incidence ~ 10 / 10⁵ catheter-days
- Screening
 - Catheter-related venous thrombosis (CRVT) is often asymptomatic, and screening is appropriate
 - Upper limb veins
 - Jugular
 - Subclavian, distal
 - Axilla
 - Arm

Performance Characteristics	Compression Ultrasound	Doppler
Sensitivity	97%	96%
Specificity	94%	96%

- In the event of a CRVT, give the indications for removal of the CVC.
 - CVC
 - Infection
 - Inclusion
 - No longer needed
 - Anti-coagulation plus
 - Progression of CRVT
 - Symptomatic pulmonary embolus



➤ Treatment

❖ Catheter thrombosis

- Heat CVC-thrombosis with anticoagulation, but
 - Do not anti-coagulate for primary prevention of thrombosis
- If CVC occluded
 - Flush with saline (0.9% NaCl)
 - Fibrinolytic drugs

❖ Catheter Occlusion

- Exclude mechanical obstruction
- Irrigation
 - Non-thrombotic

Normal saline



Directed irrigation

Cause	Irrigation solution
▪ Lipid	Ethanol 70% or NaOH (0.1 N)
▪ Mineral (CaPO ₄)	HCl (0.1 N)
▪ Drugs	
– Acidic	HCl (0.1 N)
– Basic	NaOH (0.1 N)

- Thrombotic
 - Thrombolytics
- Endoluminal branching

“Harsh words are heavy and often fall with a big thud,
but a kind word will bounce on and on...”

Anonymous



Drug Absorption in SBS

- Fat malabsorption, interruption of enterohepatic circulation
 - Cyclosporine
 - Digoxin
 - Tacrolimus
 - Warfarin
- ↓ gastric H⁺ (e.g., PPIs)
 - Antifungals
 - Antiretrovirals
 - Antibiotics (penicillins, macrolides)
- ↑ gastric H⁺ (hypersecretory states, such as after distal small bowel obstruction)
 - Alendronate
 - Digoxin
 - Nifedipine

↓ bioavailability (↓ blood concentration)

↓ bioavailability (↓ blood concentration)

↑ bioavailability (↑ blood concentration)

➤ Therapeutic Surgery

❖ Types

- Slow transit
 - Correct strictures, fistula (enteroenteritis), blind loops, obstruction
- Bowel dilated
 - ↑ motility
 - Tapering enteroplasty
 - Bianchi longitudinal intestinal lengthening [LILT]
 - Serial transverse enteroplasty (STEP)
 - Outcomes
 - Survival 70-90%
 - Off PN 70%
 - Reversal of liver disease > 80%
 - Small bowel transplantation required in ~ 5-20%
- Bowel not dilated
 - ↓ motility
 - Segmental reversal of the small bowel (SRSB)
- ↑ mucosal surface area
 - Controlled tissue expansion (CTE)

❖ Small bowel transplantation (SBTx)

List patient early for SBTx, when s/he is still stable on HPN

- Liver failure from intestinal failure-associated liver disease (IFALD)
 - ↑ bilirubin > 54-108 µmol/L (> 3-6 mg/dL)
 - Increasing
 - Thrombocytopenia
 - Splenomegaly
 - Portal hypertension, and its complications



➤ Prognosis (IF, on HPN)

5-yr Survival Rate	
○ Survival	
– Candidate for ITx	87%
– SBTx recipients	54%
– Not a candidate for ITx	
▪ HPN failure	84%
▪ High-risk underlying disease	84%
▪ High-risk morbidity IF / low acceptance of HPN	54%
○ Causes of death on HPN	RR
– Intestinal failure-associated liver disease (IFALD)	3.2
– Invasive intra-abdominal desmoid tumours	7.1
– Central venous catheter (CVC)-related complications	2.1
	(P = 0.058)
○ Combined intestinal (IT) plus liver transplantation (LT) (IT + LT)	
– Mortality	IT = IT + LT
– Graft survival	IT > IT + LT
– Death on waiting list	IT << IT + LT

“Ambition is the path to success. Persistence is the vehicle you arrive in.”

Bill Bradley

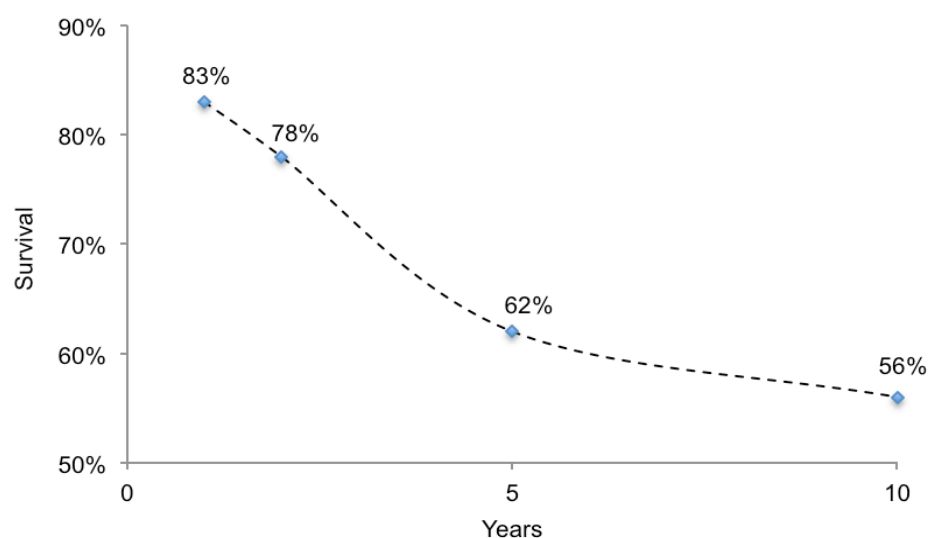


RADIATION ENTERITIS

➤ Demography

- 20% of persons receiving pelvic radiotherapy develop radiation enteritis, usually causing type III intestinal failure

➤ Prognosis



- About 1/3 of patients on HPN for RE are able to switch from HPN to oral intake

➤ Treatment

- Trial of food intake
 - If not successful, early use of enteral tube feeding → HPN

Surgical Considerations

- Multidisciplinary HPN team
- Resect smallest part of small intestine as possible
- Conserve as much colon as possible, and
 - Preserve the ileocolonic valve
 - Consider bowel lengthening procedures
- Avoid resection surgery in CIPO
 - Venting ostomy if necessary



DECREASING OSTOMY OUTPUT

- Give pharmaceutical agents, which are useful to ↓ ostomy output.
 - Gastric proton pump inhibitor (PPI)
 - ↓ gastric volume, and H^+
 - ↓ ostomy weight, and Na^+ (~20%)
 - Octreotide (somatostatin analog)
 - ↓ secretion stomach, pancreas, liver (bile)
 - ↓ Na^+ / H_2O secretion
 - ↑ Na^+ / H_2O absorption
 - ↓ motility
 - ↓ release of
 - Gastrin
 - Gastrin inhibitory peptide (GIP)
 - Vasoactive intestinal peptide (VIP)
 - Clonidine (α_2 -adrenergic agonist)
 - ↓ $NaHCO_3$ / H_2O secretion
 - ↑ Na^+ / H_2O absorption
 - ↓ motility
 - Anti-diarrheal agents
 - Loperamide, diphenoxylate, codeine, tincture of opium
 - Somatotropin (growth hormone)
 - Teduglutide (glucagon-like peptide [GLP-2])
 - ↑ intestinal wet weight absorption
 - ↓ need for parenteral fluids

“Setting goals is the first step in turning the invisible into the visible.”

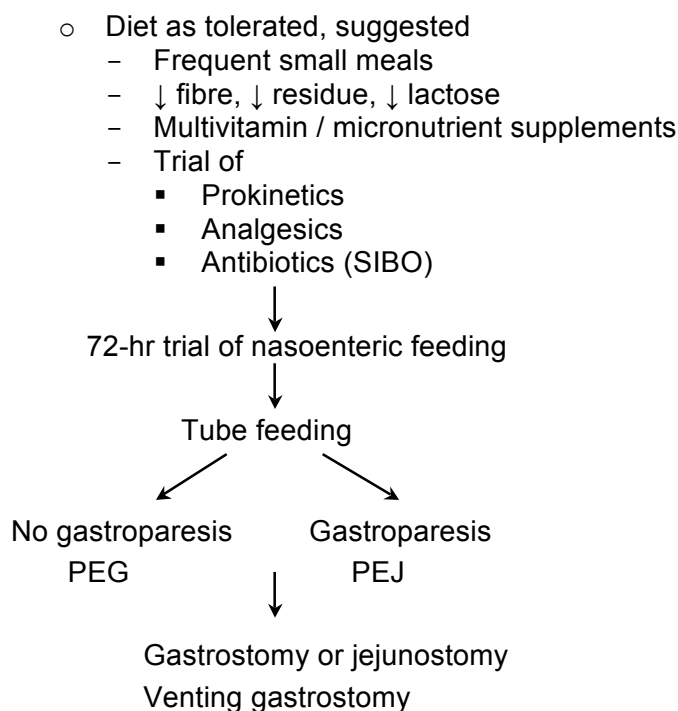
Tony Robbins



CHRONIC INTESTINAL PSEUDO-OBSTRUCTION (CIPO)

- Diet
 - Individualize
 - Prokinetics
- Enteral tube feeding / HPN
 - Use early if oral intake trial is unsuccessful
- Relapsing CIPO
 - Antibiotic cycles to eradicate possible small intestinal bacterial overgrowth (SIBO)

➤ Sequence of nutritional intake



Surgical Caution in CIPO

- ↑ risk of post-operative
 - Worsening
 - Mortality
 - Morbidity
 - Need for reoperation
- Options
 - Venting ostomy ileostomy, jejunostomy, gastrostomy



SMALL BOWEL CROHN DISEASE

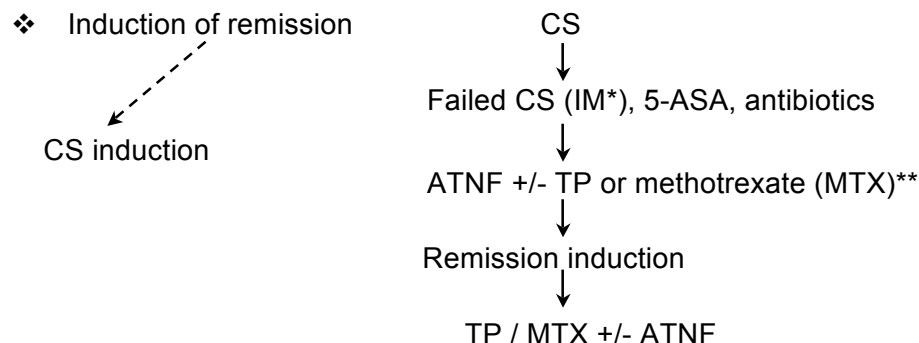
- Note
 - Please also see section on Crohn for material related to Crohn Colitis and to Ulcerative Colitis

Use of Immunomodulatory and Anti-TNF- α Drugs in Crohn Disease Moderately Severe Inflammatory –Type: AGA Guidelines

Abbreviations: AGA, American Gastrointestinal Association

Terdiman JP, et al. Gastroenterology 2013; 145: 1459-63.

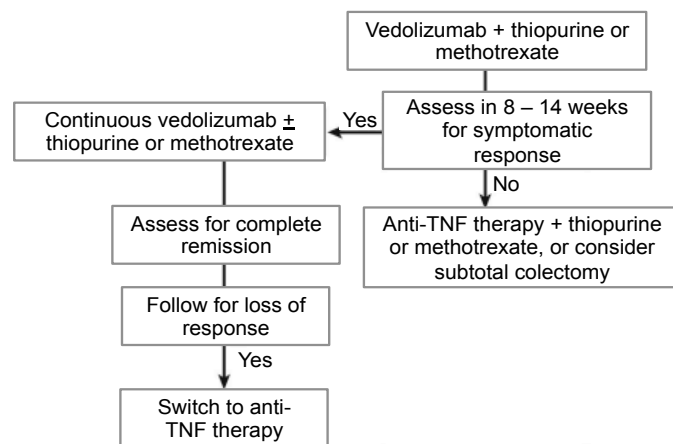
Moderately Severe “attack” (relapse) of Crohn Disease



* Induction – Do not use TP or MTX monotherapy

** Do not use in pregnancy; caution: ↑ risk of hepatic / pulmonary fibrosis

Abbreviations: ATNF, anti-tumour necrosis factors; CS, corticosteroids; IM, immunotherapy (TP, MTX); MTX, methotrexate; TP, thiopurine

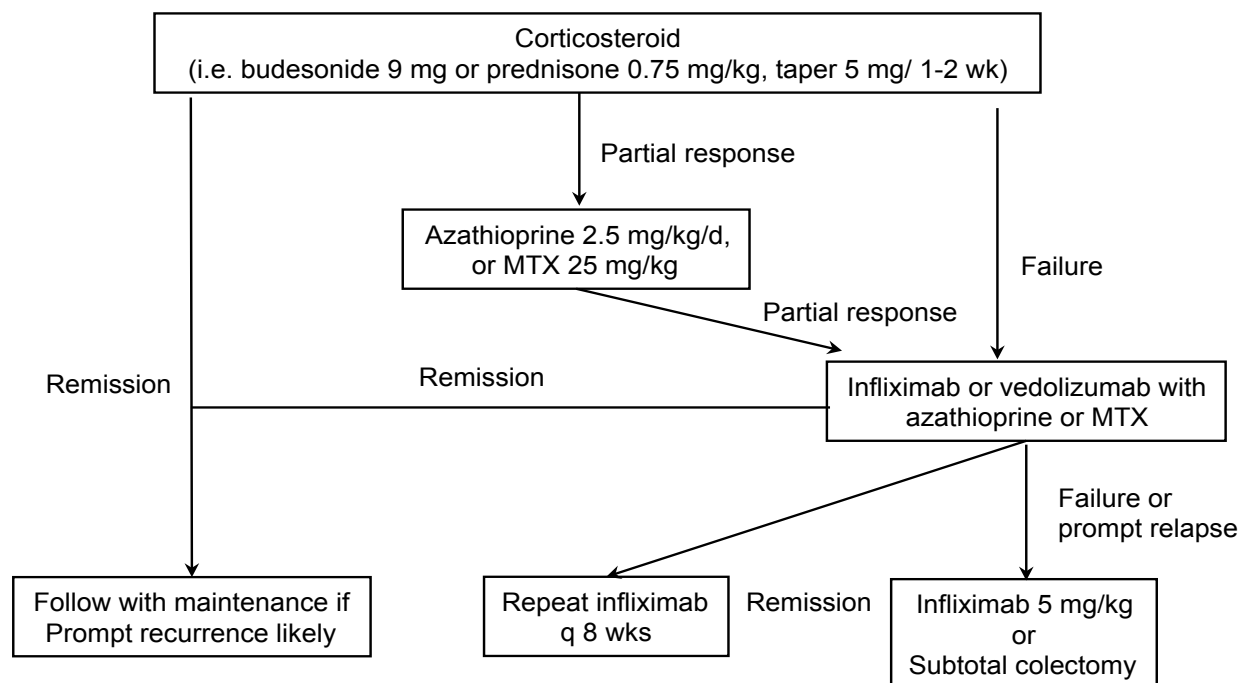


The consensus group concluded that vedolizumab is a useful option in patients who have failed to respond to corticosteroid, immunosuppressant, or anti-TNF therapy. No data are currently available regarding treatment strategies following failure of vedolizumab.

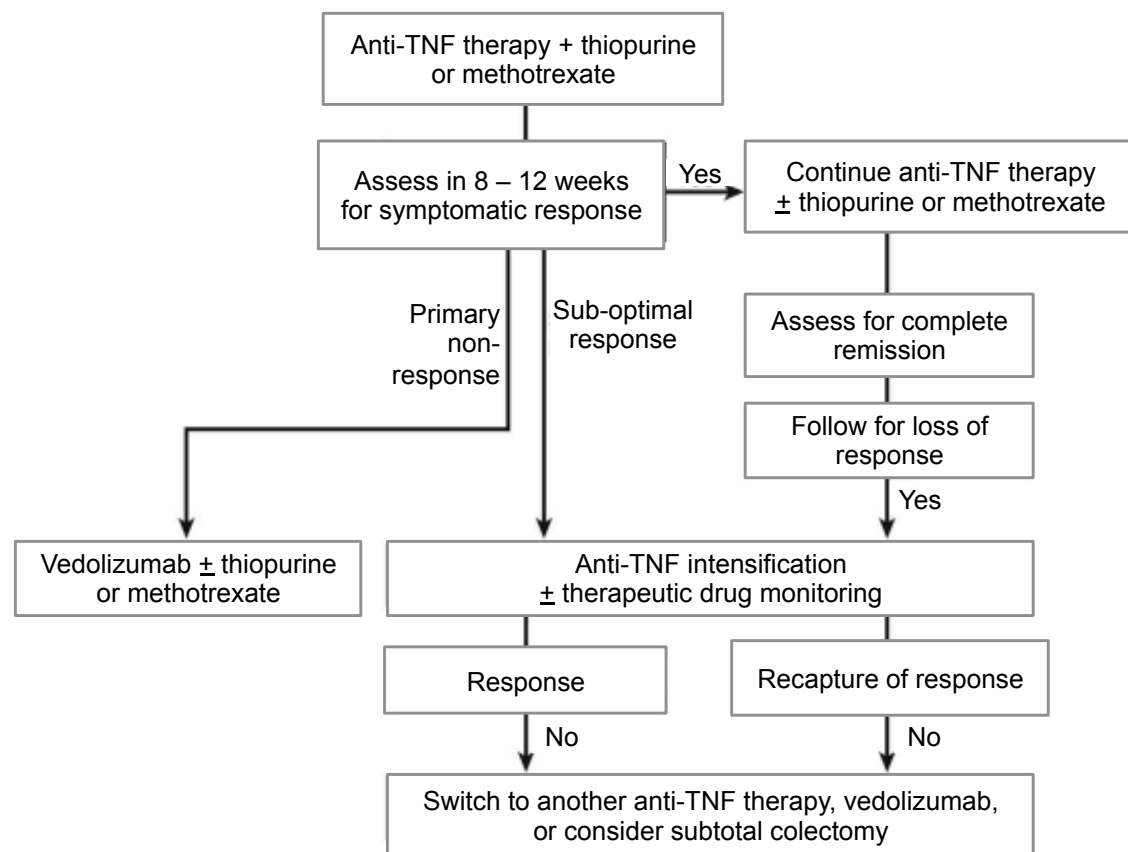
* In the induction component of the GEMINI I trial, 374 randomized patients who had previously received therapy with corticosteroids, immunosuppressants, or anti-TNF therapies were randomized to vedolizumab or placebo. At week 6, vedolizumab showed significantly higher rates of complete remission compared with placebo in patients overall (16.9% vs 5.4%; $P = 0.001$) and numerically higher rates in patients prior anti-TNF therapy (9.8% vs 3.2%), corticosteroid (21.4% vs 0%), or immunosuppressant failure (21.9% vs 10.9%). Rates of symptomatic response were significantly higher in the overall patient population (47.1% vs 25.5%; $P = 0.001$) and those with prior anti-TNF therapy (39.0% vs 20.6%) or corticosteroid failure (59.5% vs 20.0%). In patients with prior corticosteroid failure (59.5% vs 20.0%). In patients with prior corticosteroid failure, mucosal healing rates were dramatically improved with vedolizumab therapy compared with placebo (59.5% vs 24.0%). An earlier, small phase 2 dose-finding RCT found that symptomatic response rates with vedolizumab were approximately twice those of placebo (> 50% vs 22% - 33%).



Management of Crohn disease: London Guidelines (Chande N., unpublished)



Corticosteroid-resistant / dependent Crohn Disease



Management of Crohn Disease After Surgical Resection: AGA Guidelines

Abbreviation: AGA, American Gastrointestinal Association

Regueiro M, et al. Gastroenterology 2017; 152; 277-295.

➤ Risk of surgical recurrence

	Yr	%
Repeat surgical resection	1	16
	5	33
	10	47
Clinical recurrence	1	~30
Symptoms	5	~40

➤ Risk stratification

- Give the profile of the post-resection patient with Crohn disease (CD) who is at higher risk of post-operative recurrence.
 - Patient
 - Young age (< 30 yr) at diagnosis of CD
 - Early surgery
 - < 10 yr interval between CD diagnosis and surgery
 - Smoking
 - Surgery
 - ≥ 2 previous CD-related surgeries
 - Disease
 - Perianal
 - Long resection
 - Begin pharmacological therapy soon after surgical resection to ↓ risk of asymptomatic endoscopic recurrence (AER) and symptomatic clinical recurrence (SCR) at 102 wk

RR	↓ in recurrence per 10 ³ patients	
	Low Risk	High Risk
- AER		
▪ 0.91, 95% CI, 0.59 - 1.42	27	72
- SCR		
▪ 0.83, 95% CI, 0.46 - 1.50	34	85



- The choice of drugs to begin early after surgical resection include α -TNF, TP or antibodies

Drug	$\downarrow$ in recurrence per 10 ³ patients vs non-early drug prophylaxis	
	Low Risk	High Risk
- TNF		
▪ AER	207	310
▪ SCR	87	162
- Antibiotics		
▪ AER	135	152
▪ SCR	85	158
Thiopurine	Relative Effect (95% CI)	
	AER	SCR
- vs 5-ASA	0.56 (0.31 – 1.01)	0.73 (0.45 – 1.18)
- vs antibiotics	0.94 (0.19 – 4.57)	0.90 (0.29 – 2.77)
- TP plus antibiotics		
▪ vs 5-ASA	0.28 (0.04 – 1.76)	0.28 (0.04 – 1.76)
▪ vs α -TNF	0.47 (0.14 – 1.38)	0.48 (0.04 – 5.65)

Abbreviations: CI, confidence interval; RR, relative risk; TP, thiopurines (azathioprine [AZA], 6-mecaptopurine [6-MP])

“...thiopurine monotherapy... probably result in the largest reductions in disease recurrence”, with approximately comparable adverse events without the α -TNF associated burden of infusion / injection site reactions, demyelinating disease, or worsening heart failure.”

- Serious adverse events (AEs, infection, malignancy, intolerance, discontinuing therapy)

Adverse Events	α -TNF	TP (AZA, 6-MP)
Infection	~8	10
Malignancy	4	0.75
Intolerance	10	18



- In the post-operative CD patient who receives early prophylactic pharmacotherapy, the risk of relapse can be reduced further with endoscopy at 6 and 12 months to guide further management based on the endoscopic findings

Active Management	Recurrence per 10 ³ patients, vs no Endoscopic Monitoring	
	Low Risk	High Risk
– Guided by scheduled (routine) endoscopy		
▪ AER	81	210
▪ SCR	36	81

Note

- “An active management strategy involving routine endoscopic monitoring with treatment step-up” ...allows for endoscopic remission to be recaptured in 38% of patients.”

Abbreviations: AER, asymptomatic endoscopic recurrence of Crohn disease; SCR, symptomatic clinical recurrence.

Take-Home Message

Start prophylactic therapy with thiopurine (azathioprine, 6-mercaptopurine), anti-TNF or antibiotics soon after surgical resection of Crohn disease, and follow patient with post-operative endoscopy to adjust the continued pharmacotherapy

“When originality may not be genuine, check it on
“Turn it in.com”. Even Deans deviate.

Grandad



Preventive Care in IBD: ACG Guidelines

Abbreviation: ACG, American College of Gastroenterology

Farraye FA, et al. Am J Gastroenterol 2017; 111: 241-258.

❖ Vaccinations

➤ Guiding principles for vaccination of patients with IBD

- Immunosuppressed patients with IBD
 - Should not receive live vaccines (give live vaccines ≥ 4 wk before starting immunosuppression)
 - Should receive non-live vaccines $\geq$ wk before starting immunosuppression, but their immune response to the non-liver vaccines may be reduced and boosters may be necessary
- For further infection, please consult
 - <http://www.stelarainfo.com/pdf/prescribinginformation.pdf>
 - <http://cornerstonehealth.org/checklist/>
 - <http://www.ccfa.org/science-and-professionals/programs-materials/ccfa-health-maintenance.pdf>

➤ Recommendations

❖ Live vaccines

- Measles, mumps, rubella (MMR)
 - If IBD patient's previous vaccination status is not known, check titre for MMR before vaccination
 - If vaccination / revaccination necessary, vaccinate at least 6 wk before starting immunosuppression
 - Vaccination program
 - 2 doses ≥ 4 wk apart
 - If already on immunosuppression, do **not** vaccinate
 - Family members must receive vaccination
- Varicella (VZV)
 - If IBD patient's previous vaccination status is not known, check titre for varicella antibody before vaccination
 - If vaccination / revaccination necessary, vaccinate 1-3 mon before starting immunosuppression
 - Vaccination program
 - If already on immunosuppressant, decision to vaccinate is on patient-by-patient basis
 - 2 doses, 6 weeks apart
 - Family members
 - Should receive vaccination
 - If IBD patient develops rash with vaccination, they should avoid contact with family until vesicles disappear
- Herpes zoster
 - When IBD patient ≥ 50 yr, give 1 does of vaccine at least 4 wk before starting immunosuppression
 - If already on immunosuppressant, decision to vaccinate is on a patient-by-patient basis



- Family members
 - Should receive vaccine
 - If IBD patient develops rash with vaccination, they should avoid contact with family until rash disappears
 - If low-level immunosuppression, may consider HZV vaccination
 - Prednisone 20 mg/d, and within 3 mon after stopping
 - Alternate dose corticosteroids
 - Methotrexate ≤ 2.4 mg/kg per wk, and within 3 mon of stopping
 - Azathioprine ≤ 3 mg/kg per day, or 6-mercaptopurine ≤ 1.5 mg/kg per day and within 3 mon of stopping
- Yellow fever
 - Liver attenuated vaccine which when given to an immune suppressed IBD patient, may cause multiorgan failure and death
 - If necessary to vaccinate, do so 3 mon before starting anti-TNF therapy

❖ Inactive vaccines

- All IBD patients
 - Tdap (diphtheria, tetanus, pertussis [Corynebacterium diphtheria, Clostridium tetanus, Bordetella pertussis])
 - HAV (hepatitis A virus) vaccination
 - 2 doses vaccination at 0 and 6 mon
 - HBV (hepatitis B virus)
 - 1 dose age 11-64 yr; booster q 10 yr
 - 3 doses at 1 mon, 2 mon, 4-6 mon, then check titre 1 mon after 3rd dose
 - At 1-3 mon after HBV vaccinated test for HBsAb
 - If no HBV antibody response (HBsAb) < 10 to 100 IU/L
 - Revaccinate with usual or double dose, or
 - Vaccinate with 3 doses, or with combined HAV + HBV
 - Haemophilus influenza B
 - < 65 yr trivalent inactivated influenza vaccine
 - ≥ 65 yr "high dose" vaccine
 - Do not give live attenuated influenza vaccine to immunosuppressed IBD patients
 - Anti-TNF plus thiopurine $\rightarrow$ $\downarrow$ serological response
 - Household contacts of IBD immunosuppressed patients $\rightarrow$ give trivalent inactive vaccine
 - Streptococcus pneumonia
 - No previous S. pneumonia vaccination
 - PCV13, then 2-12 mon later give PPSV23
 - Previous PPSV23
 - Give PCV13 ≥ 1 yr after PPSV23, then give second dose of PPSV23 ≥ 5 yr after initial PPSV, then repeat PPSV23 at 5 yr if patient ≥ 65 yr

Abbreviations: PCV, pneumococcal conjugate; PPSV, pneumococcal polysaccharide vaccine



- Give the pharmacologicals which are associated with ↑ risk of pneumococcal infection in persons with IBD.
 - Narcotics
 - Proton pump inhibitors (PPIs)
 - Corticosteroids
 - Thiopurines
 - Biological
- Clinical Caution

IBD patients hospitalized with pneumonia are at ↑ risk of death during their stay in hospital.
- Poor Vaccination Response

IBD patients treated with anti-TNF plus a thiopurine or methotrexate have response to vaccination to PPSV23, but not when they are taking just an anti-TNF.
- HPV
 - Female and males age 11-26 yr
 - 3 doses at 0, 2 and 6 mon
 - Meningococcal disease
 - Vaccinate IBD patients age 16-23 who are high risk persons (please see Kim DK, et al. Ann Intern Med 2016; 164: 184-194)
- Vaccination of Healthy Household Contacts of IBD Patients who are Immunosuppressed
- Inactive / liver vaccinations should be up-to-date (MMR, varicella, zoster, rotavirus)
 - If the household member develops skin rash from varicella or zoster, the IBD patient must avoid contact with the family member until their skin lesions disappear
 - If the household member infant / child has been vaccinated for rotavirus, the IBD patient must not handle the child's diaper for 4 wk
 - Influenza
 - Give annually to all household contacts except babies < 6 mon of age
 - Use inactive vaccines (may also use attenuated vaccine if household recipient is 2-49 years of age, are healthy and are not pregnant)

Please apply these principles to the patients who are immunosuppressed with other GI / Hepatology conditions, such as Ulcerative Colitis (page 70) or Autoimmune Hepatitis (page 242).

➤ Screening

❖ Osteoporosis

- Osteoporosis on DEXA Scan is common (~25%) in persons with IBD, but fragility fractures are not common
- The presence of active inflammation does not predict the presence of osteoporosis, and there are numerous other confounding risk factors such as smoking, use of corticosteroids, and reduced intake of calcium and vitamin D
- Guidelines suggest screening IBD patient for osteoporosis if
 - Previous fragility fractures
 - Age > 65 in women, > 70 in men
 - Use of prednisone ≥ 7.5 mg per day for > 3 consecutive months



❖ Depression and Anxiety

- There is ↑ anxiety and depression in patients with IBD (~20% versus central population of ~10%)
- Anxiety and depression
 - ↑ active disease (hazard ratio 2.27)
 - ↑ risk of
 - ↑ number of relapses over 12-18 mon
 - ↓ time to relapse
 - ↓ response to treatment
- Perceived stress and avoidance coping predicts early relapse (hazard ratio 7.0)
- Use of anti-depressants in IBD
 - ↓ psychological symptoms
 - ↓ somatic symptoms

❖ Smoking

- Give the adverse effects of cigarette smoking to persons with Crohn disease (CD).
 - ↑ risk
 - Progression
 - Development of
 - Arthropathy
 - Strictures
 - Perianal disease
 - Developing Crohn disease (CD)
 - Risk of flare active disease before / after surgery
 - Need for corticosteroids / thiopurines
 - Need for surgery and for respiration
 - Stopping smoking
 - ↓ risk of recurrence

❖ Cancer

Cervical Cancer

- All women and men aged 9-26 yr should receive HPV vaccination, but
- All female IBD patients (UC and CD), even those immunized with HPV, and who are immunosuppressed, should have an annual cervical pap smear because of their ↑ risk of high-grade cervical dysplasia and cancer

Melanoma and Non-melanoma Skin Cancer

- There is risk (37%) of non-melanoma skin cancer (NMSC) as well as melanoma skin cancer (MSC) in IBD patients who are immune suppressed
- The risk of NMSC (SCC, BCC) may ↑ with duration of thiopurine use
 - Thiopurine, anti-TNF for > 1 yr
 - NMSC (squamous and basal cell carcinomas [SCC, BCC])
 - Anti-TNF
 - MSC
- The risk of NMSC (SCC, BCC) may with ↑ duration of thiopurine use

Screening Cautions

- Dermatological surveillance and sun protection (clothing, sunscreen) for MSC should occur in all IBD patients (whether on, off or never on anti-TNFs, thiopurines).



Management of Crohn Disease (CD) After Surgery: AGA Guidelines

Abbreviation: AGA, American Gastrointestinal Association

Nguyen GC, et al. Gastroenterology 2017; 152: 271-275.

Please note that the interpretation of data that informed these recommendations was consistent with the technical review

Low risk of recurrence, or patient preference/values

- No pharmacological prophylaxis

- Ileocolonoscopy at 6-12 mon

Endoscopic recurrence (Rutgeerts ≥ i2)

- Anti-TNF and/or thiopurine

- CD requirement for surgery
 - 50% within first 10 yr
- Recurrence after surgery
 - 25% within 5 yr
 - Endoscopic
 - 90% within 1 yr
 - Surgical
 - 25% within 5 yr

- High-risk of recurrence (3 P's)
 - Short duration of CD
 - < 30 yr old
 - Penetrating CD (+/- perianal disease)
 - Prior resections
 - "Puffing" (smoking)

Surgically-induced CD remission

High risk of recurrence

- Pharmacological prophylaxis
 - Anti-TNF +/-
 - Thiopurine ±
 - Nitroimidazole (3 mon)

Patient preference or intolerance to anti-TNF and thiopurine
Nitroimidazole antibiotics

- Ileocolonoscopy at 6-12 mon

Endoscopic recurrence (Rutgeerts ≥ i2)

- Optimize or add thiopurine / anti-TNF

- Purpose of ileocolonoscopy
 - Detection of "endoscopic recurrence" triggers escalation of therapy: no validated scoring system available.

"Postoperative Criteria Endoscopic Recurrence (POCER) Trial" Endoscopic step-up vs Standard of Care (continue pharmacological strategy started in early post-op period)

Relative Reduction in Clinical Endoscopic Recurrence

○ AZA, anti-TNF	~60%
○ Metronidazole	50%



COLON



INFLAMMATORY BOWEL DISEASE

- Note: for information on non-colonic Crohn disease, including some considerations related to ulcerative colitis, please see section on Small Bowel, Crohn disease, page 59).

The Role of Endoscopy in Inflammatory Bowel Disease (IBD): ASGE Guidelines

Abbreviations: ASGE, American Society for Gastrointestinal Endoscopy

Shergill AK, et al. Gastrointestinal Endoscopy 2015; 81(5): 1101-20.

- ❖ Ulcerative Colitis (UC) / Crohn Colitis (CC) ¹
 - Colonoscopy to evaluate IBD for diagnosis and staging
 - Routinely use a validated staging system and disease extent ²
 - Sigmoidoscopy performed if contraindication to colonoscopy
- ❖ Crohn disease
 - Evaluate small bowel with VCE after establishing patency (patency capsule, SBFT, CTE, MRE) when findings would influence decision-making
 - EUS to investigate and to manage perianal disease
- Indications to perform colonoscopy
 - Pouch symptoms
 - Post-operative (6-12 mon) for risk stratification
 - After 8 yr of UC or Crohn colitis (CC), then
 - q 1-3 yr for disease in sigmoid colon and proximally
 - Chromendoscopy recommended to target biopsies
 - Biopsies
 - 2 from each colon segment, or
 - 4 quadrant q 10 cm (≥ 33 biopsies), if poor bowel preparation, active colitis or pseudopolyposis
 - May combine random plus targeted biopsies
 - Dysplastic polypoid / non-polypoid lesion removed endoscopically undertake endoscopic surveillance at 1-6 mon, then q 1 yr
- Treatment
 - Endoscopic balloon dilation
 - Benign strictures < 4 cm
 - Proctocolectomy
 - Dysplastic lesion
 - At base of lesion
 - Detected but not endoscopically resectable
 - Invisible (random biopsy) at chromendoscopy, with either HGD or multifocal LGD

¹ When > 1/3 of colon affected by CC

² See Shergill AK, et al. Gastrointestinal Endoscopy 2015; 81(5): 1101-1120.

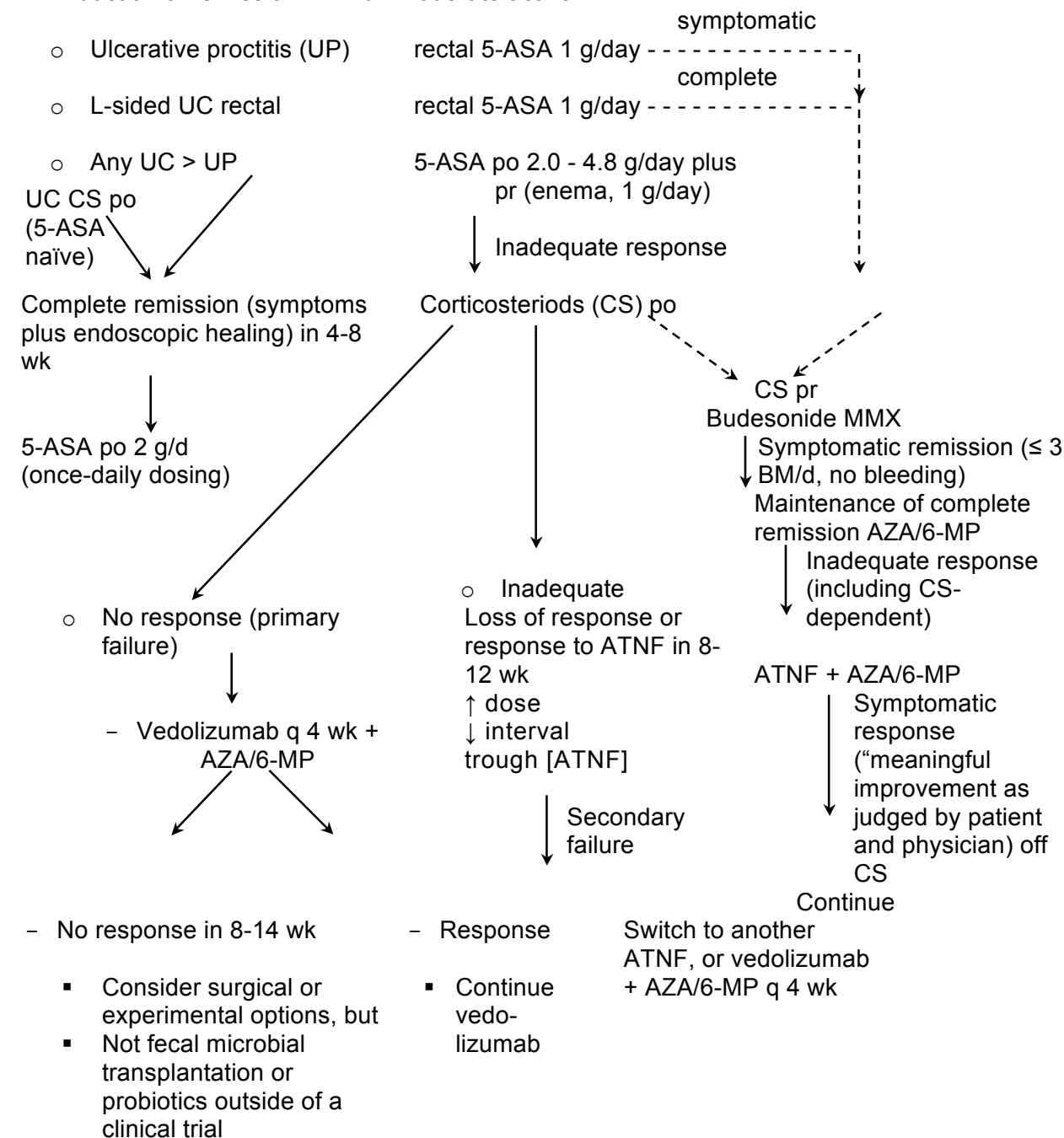
Abbreviations: CTE, CT enterography; EUS, endoscopic ultrasound; HGD, high-grade dysplasia; LGD, low-grade dysplasia; MRE, MR enterography; SBFT, small bowel (barium) follow through; VCE, videocapsule endoscopy



Medical Management of Non-hospitalized Patient with Mild / Moderate Ulcerative Colitis: The Toronto Consensus Guidelines

Bressler B, Marshall JK, et al. Gastroenterology 2015; 148: 1035-58.

❖ Induction of remission in mild / moderate active

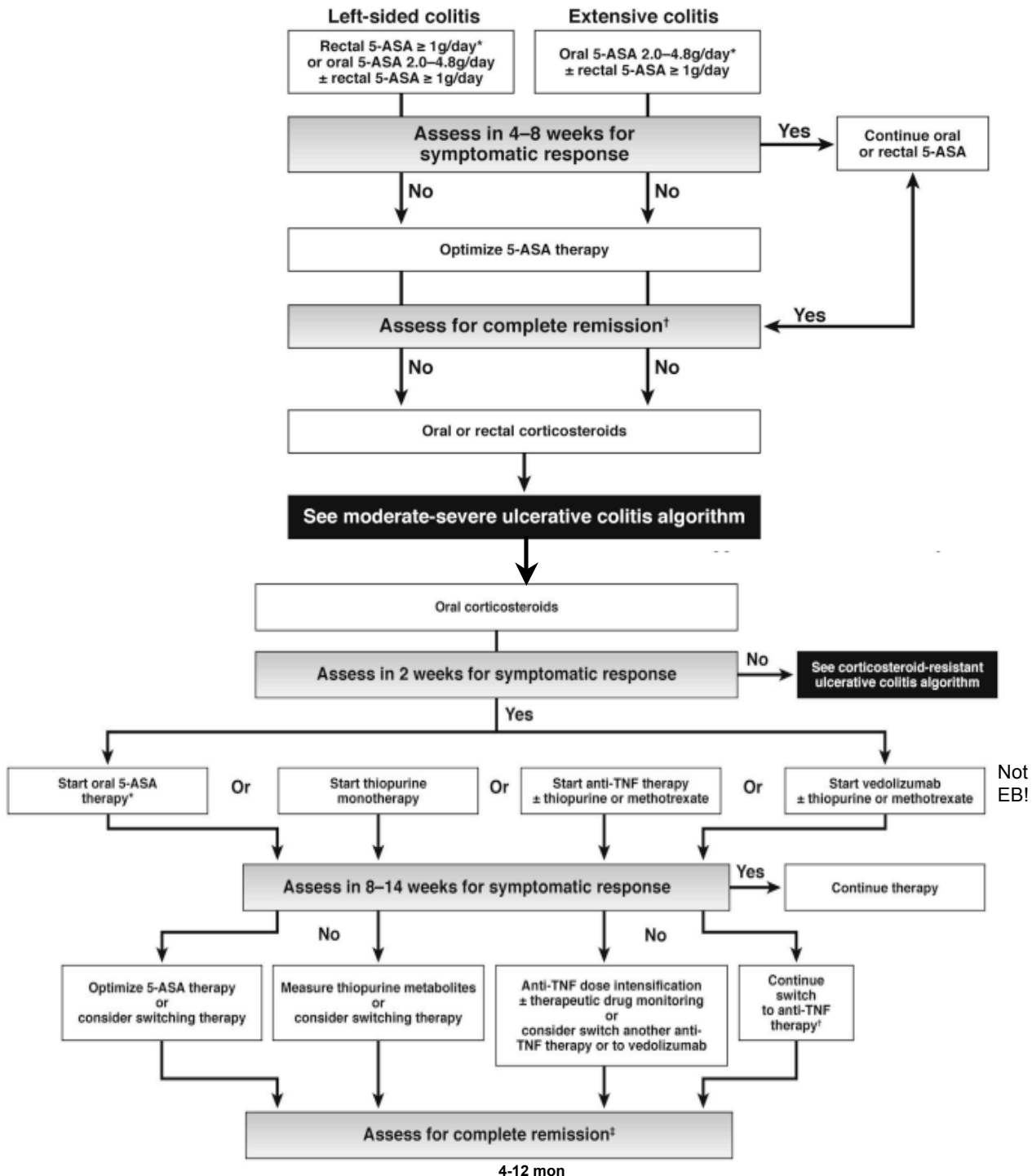


Terms: Endoscopic healing; Mayo score 0-1, normal mucosa; Primary failure of biologics, “inability of the patient to achieve corticosteroid-free complete remission despite dose optimization”; Secondary failure, “inability of the patient to maintain corticosteroid-free complete remission after achieving a symptomatic response”

Abbreviations: ATNF, antitumour necrosis factor; AZA, azathioprine; 6-MP, 6-mercaptopurine



Management of Mild to Moderate Active UC: The Toronto Consensus



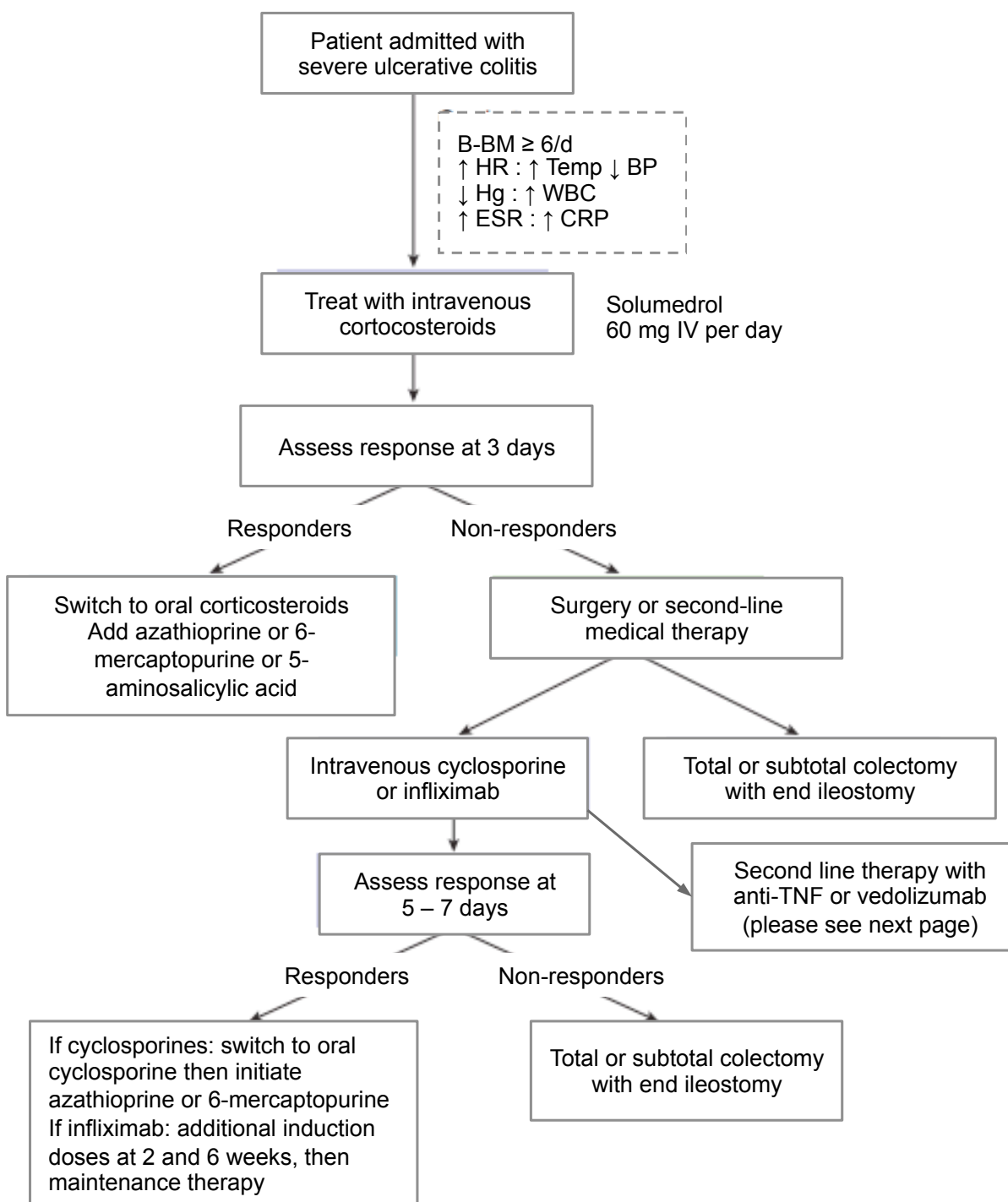
Not
EB!

Abbreviation: not EB, not evidence-based

Printed with permission: Bressler B, et al. clinical practice guidelines for the medical management of non-hospitalized ulcerative colitis: The Toronto Consensus. Gastroenterology 2015; 148: 1035-1105, Figures 5 and 6.



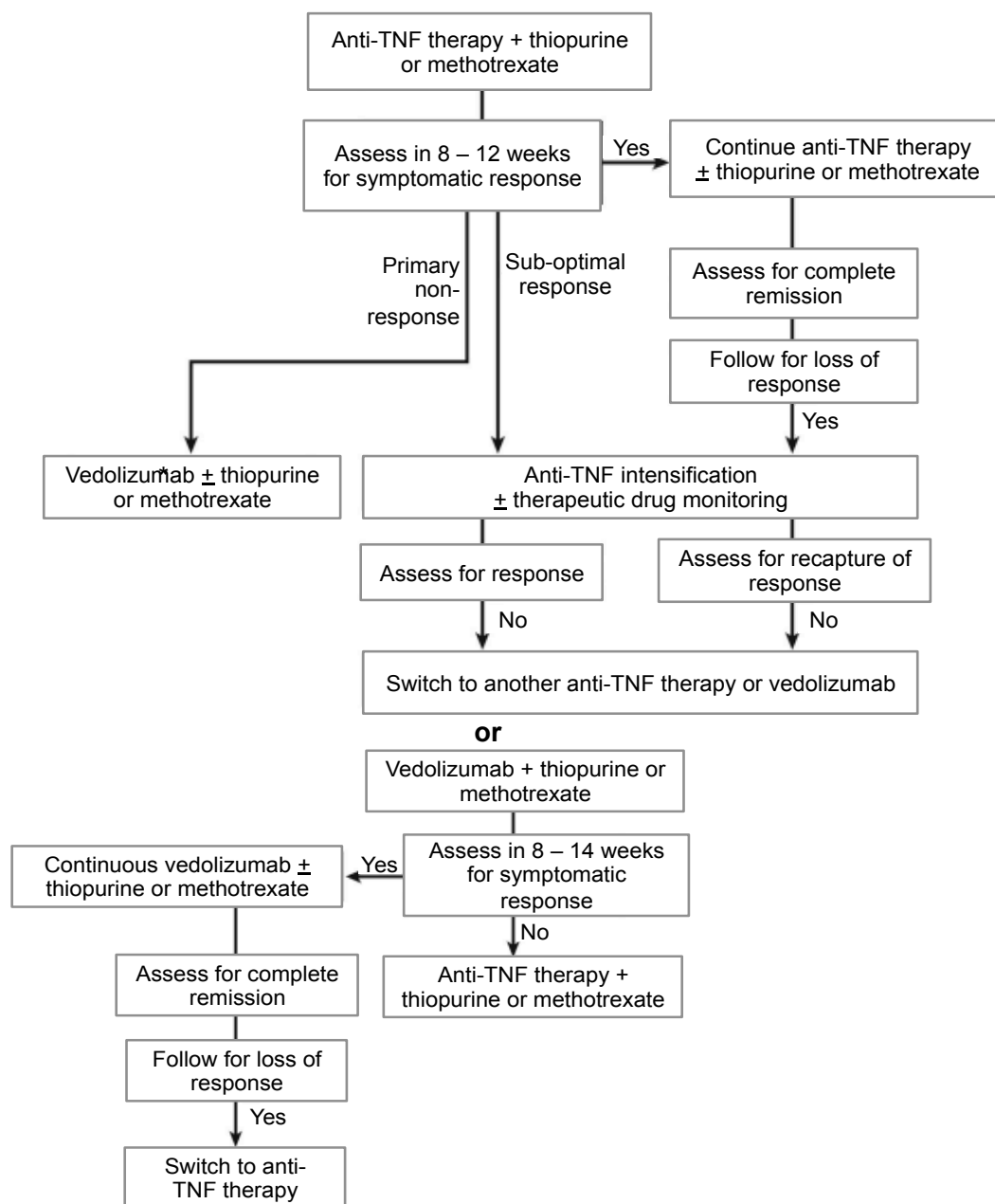
Medical Management of Hospitalized Patients with Acute Severe Ulcerative Colitis: The Toronto Consensus



Bitton A, et al. Am J Gastroenterol. 2012; 107(2): 179-94.

Printed with permission: Bitton A, et al. Am J Gastroenterol. 2012; 107(2): 179-94.





* In the induction component of the GEMINI I trial, randomized patients who had previously received therapy with corticosteroids, immunosuppressants, or anti-TNF therapies were randomized to vedolizumab or placebo. At week 6, vedolizumab showed significantly higher rates of complete remission compared with placebo in patients overall (16.9% vs 5.4%; $P < 0.001$) and numerically higher rates in patients with prior anti-TNF therapy (9.8% vs 3.2%), corticosteroid (21.4% vs 0%), or immunosuppressant failure (21.9% vs 10.9%). Rates of symptomatic response were significantly higher in the overall patient population (47.1% vs 25.5%; $P < .001$) and those with prior anti-TNF therapy (39.0% vs 20.6%) or corticosteroid failure (59.5% vs 20.0%). In patients with prior corticosteroid failure, mucosal healing rates were dramatically improved with vedolizumab therapy compared with placebo (59.5% vs 24.0%). An earlier, small phase 2 dose-finding RCT found that symptomatic response rates with vedolizumab were approximately twice those of placebo (>50% vs 22% - 33%).

Printed with permission: Bressler B, et al. Gastroenterology 2015; 148: 1035-1105, Figure 7.



- General care
 - IV fluids
 - Stool cultures
 - Including *C. difficile*
 - Abdominal radiograph
 - Chest x-ray
 - Consider flexible sigmoidoscopy plus mucosal biopsies
 - Normal oral diet, or enteral nutrition if normal diet not tolerated
 - VTE prophylaxis with heparin / LMNH
 - Avoid narcotics and routine antibiotics
- Note:
- ¹ CRP often recommended, since it may be a better marker of suboptimal response
 - ² Some authorities suggest non-response to IV corticosteroids be determined on day 3-5
 - ³ Some authorities suggest non-response be defined as lack of a 50% ↓ BM and laboratory; colectomy represents total colectomy or colectomy plus end colostomy
 - ⁴ Many authorities recommend that AZA or 6-MP be given with IFX to ↓ production of antibodies to IFX and ↓ response; more recent studies suggest ↑ success starting with IFX 10 mg/kg
 - Tuberculin skin test or interferon γ releasing assay (HBV, HIV infection)*
- Do not use thiopurine monotherapy to induce complete remission. GRADE: Strong recommendation, low-quality evidence.
 - In selected patients with UC who have achieved symptomatic remission on oral corticosteroids, use thiopurine monotherapy as an option to maintain complete corticosteroid-free remission.
 - Do not use methotrexate monotherapy to induce or maintain complete remission. Strong recommendation, low-quality evidence for induction and maintenance
 - When starting anti-TNF therapy to induce complete remission use the anti-TNF therapy with a thiopurine or methotrexate rather than used as monotherapy.

Abbreviations: 6-MP, 6-mercaptopurine; AZA, azathioprine; CRP, C reactive protein; ESR, erythrocyte sedimentation rate; HBV, hepatitis B virus infection; HIV, human immunodeficiency virus infection; IFX, infliximab; PUCAI, pediatric UC activity index; VTE, venous thromboembolism

➤ Definition

- Complete remission – Both symptomatic remission and endoscopic healing as defined below
- Endoscopic healing – Normal mucosa, vascular blurring, or chronic changes (e.g., inflammatory polyps, scarring) without friability
- Symptomatic remission – Normal stool frequency (< 3/day) and no blood in the stool
- Symptomatic response – Meaningful improvement in symptoms as judged by both the patient and physician in the absence of remission; response should not be considered a desirable final outcome but is useful to assess early response to treatment

➤ Background



5-ASA

- In patients with mild to moderate active ulcerative proctitis, we recommend rectal 5-ASA, at a dosage of 1 g daily, as first-line therapy to induce symptomatic remission. GRADE: Strong recommendation, high-quality evidence.
- In patients with mild to moderate active left-sided UC, we recommend 5-ASA enemas, at a dosage of at least 1 g daily, as an alternative first-line therapy to induce complete remission. GRADE: Strong recommendation, moderate-quality evidence.
- In patients with mild to moderate active UC of any disease extent beyond proctitis, we recommend an oral 5-ASA preparation, at dosages between 2.0 and 4.8 g/day, as an alternative first-line therapy to induce complete remission. GRADE: Strong recommendation, moderate-quality evidence.
- In patients with mild to moderate active UC of any disease extent beyond proctitis, we suggest the combination of a rectal and an oral 5-ASA preparation over oral 5-ASA alone as an alternative first-line therapy to induce complete remission. GRADE: Weak recommendation, low-quality evidence.
- We recommend that patients with UC be evaluated for lack of symptomatic response to oral / rectal 5-ASA induction therapy in 4 to 8 weeks to determine the need to modify therapy. GRADE: Strong recommendation, very low-quality evidence.
- In patients with oral or rectal 5-ASA-induced complete remission of mild to moderate active left-sided UC or proctitis, we recommend the same therapy be continued to maintain complete remission. GRADE: Strong recommendation, moderate-quality evidence.
- In patients with oral 5-ASA-induced complete remission of mild to moderate active UC of any disease extent, we recommend continued oral therapy of at least 2 g/day to maintain complete remission. GRADE: Strong recommendation, moderate-quality evidence.
- In selected 5-ASA-naïve patients with UC who have achieved symptomatic remission on oral corticosteroids, we suggest an oral 5-ASA preparation of at least 2 g/day while being assessed for corticosteroid-free complete remission. GRADE: Weak recommendation, very low-quality evidence.
- In patients with UC who have failed to respond to oral 5-ASA, we recommend against switching to another oral 5-ASA formulation to induce remission. GRADE: Strong recommendation, low-quality evidence.
- When using oral 5-ASA to induce or maintain complete remission of UC, we suggest once-daily over more frequent dosing. GRADE: Weak recommendation, moderate-quality evidence.



Corticosteroids

- In patients with moderate to severe active UC, we recommend oral corticosteroids as first-line therapy to induce complete remission. GRADE: Strong recommendation, moderate-quality evidence.
- In patients with mild to moderate active UC who fail to respond to 5-ASA therapy, we recommend oral corticosteroids as second-line therapy to induce complete remission. GRADE: Strong recommendation, low-quality evidence.
- In patients with mild to moderate active left-sided UC or proctitis who fail to respond to rectal 5-ASA therapy, we suggest rectal corticosteroids as second-line therapy to induce complete remission. GRADE: Weak recommendation, overall very low-quality evidence.
- In patients with UC, we recommend against the use of oral corticosteroids to maintain complete remission because they are ineffective for this indication and their prolonged use is associated with significant adverse effects. GRADE: Strong recommendation, moderate-quality evidence.
- In patients with mild to moderate UC of any disease extent, we suggest oral budesonide MMX as an alternative first-line therapy to induce complete remission. GRADE: Weak recommendation, high-quality evidence.
- We recommend that patients with UC be evaluated for lack of symptomatic response to corticosteroid induction therapy within 2 weeks to determine the need to modify therapy. GRADE: Strong recommendation, very low-quality evidence.

Immunosuppressants

- In patients with UC, we recommend against the use of thiopurine monotherapy to induce complete remission. GRADE: Strong recommendation, low-quality evidence.
- In selected patients with UC who have achieved symptomatic remission on oral corticosteroids, we suggest thiopurine monotherapy as an option to maintain complete corticosteroid-free remission. GRADE: Weak recommendation, low-quality evidence.
- In patients with UC, we recommend against the use of methotrexate monotherapy to induce or maintain complete remission. GRADE: Strong recommendation, low-quality evidence for induction and very low-quality evidence for maintenance.

Anti-TNF therapy

- In patients with UC who fail to respond to thiopurines or corticosteroids, we recommend anti-TNF therapy to induce complete corticosteroid-free remission. GRADE: Strong recommendation, high-quality evidence.
- When starting anti-TNF therapy, we recommend it be combined with a thiopurine or methotrexate rather than used as monotherapy to induce complete remission. GRADE: Strong recommendation, moderate-quality evidence for azathioprine and very low-quality evidence for methotrexate.
- In patients with UC who are corticosteroid dependent, we recommend anti-TNF therapy to induce and maintain complete corticosteroid-free remission. GRADE: Strong recommendation, very low-quality evidence.



- We recommend that patients with UC be evaluated for lack of symptomatic response to anti-TNF induction therapy in 8 to 12 weeks to determine the need to modify therapy. GRADE: Strong recommendation, low-quality evidence.
- In patients with UC who respond to anti-TNF induction therapy, we recommend continued anti-TNF therapy to maintain complete remission. GRADE: Strong recommendation, very low-quality evidence for infliximab and adalimumab and high-quality evidence for golimumab.
- In patients with UC who have a suboptimal response to anti-TNF induction therapy, we recommend dose intensification to achieve complete remission. GRADE: Strong recommendation, very low-quality evidence.
- In patients with UC who lose response to anti-TNF maintenance therapy, we recommend optimizing dose to recapture complete remission. GRADE: Strong recommendation, very low-quality evidence.
- We recommend that dose optimization for patients with UC be informed by therapeutic drug monitoring. GRADE: Strong recommendation, low-quality evidence.

Other agents

- In patients with primary failure to an anti-TNF therapy, we recommend switching to vedolizumab over switching to another anti-TNF therapy to induce complete corticosteroid-free remission. GRADE: Strong recommendation, very low-quality evidence.
- In patients with secondary failure to an anti-TNF therapy, we recommend switching to another anti-TNF therapy or vedolizumab based on therapeutic drug monitoring results to induce complete corticosteroid-free remission. GRADE: Strong recommendation, very low quality evidence.
- In patients with moderate to severe active UC who fail to respond to corticosteroids, thiopurines, or anti-TNF therapies, we recommend vedolizumab to induce complete corticosteroid-free remission. GRADE: Strong recommendation, moderate-quality evidence.
- We recommend that patients with UC be evaluated for lack of symptomatic response to vedolizumab induction therapy in 8 to 14 weeks to determine the need to modify therapy. GRADE: Strong recommendation, very low-quality evidence.
- In patients with UC who respond to vedolizumab, we recommend continued vedolizumab therapy to maintain complete corticosteroid free remission. GRADE: Strong recommendation, moderate-quality evidence.
- In patients with UC, we recommend against fecal microbial transplant to induce or maintain complete remission outside the setting of a clinical trial. GRADE: Strong recommendation, low-quality evidence.
- In patients with UC, we recommend against probiotics to induce or maintain complete remission outside the setting of a clinical trial. GRADE: Strong recommendation, very low-quality evidence.

Source: Bressler B, et al. Gastroenterology 2015; 148: 1035-1105.



Biological Therapy in IBD: WCG Guidelines

Abbreviation: WCG, World Congress of Gastroenterology

D'Haens GR, et al. Am J Gastroenterol 2011; 106: 199-212.

❖ Indications for biological therapy in IBD

- High risk of severe disease
 - Young at presentation
 - Initial need for CS
 - Disease
 - Proximal (stomach, jejunum)
 - Perineum (fistulizing CD)
- Absence of
 - Fibrostenotic disease
 - Abscess
 - HBV, HIV, TB latent infection
 - Liver vaccines in last 3 mon
 - Malignancy (except NMSC)
 - Lymphoproliferative disorder
 - Demyelinating neurological disease
 - Severe heart failure
- Failure of
 - Appropriate dose / duration (including Cs-dependent) of course of CS, immunomodulators in CD
 - In UC
 - Severe acute UC not responding to 3-5 days IV CS
- Severe toxic UC
 - > 38.6°C
 - HR > 100 bpm
 - Hg < 10 g/dL
 - WBC > 10,500 /mm³
 - Albumin < 3 g/dL
 - Transverse colon > 6 cm toxic megacolon
- Severe / non-responsive CD
- Severe toxic UC for remission IFX
 - For remission IFX 5-10 mg/d at time 0, 2, 6 wk
- Good response
 - Early luminal CD
 - More likely with ↑ CRP
- Suboptimal IFX response
 - ↑ dose to 10 mg/kg, or
 - ↓ dosing interval
 - Surgical consultation (now or earlier)
- Switch to adalimumab, certolizumab or second-line natalizumab
- CD
 - Maintenance
 - Avoid combination therapy with Natalizumab, and consider avoiding AZA in young IBD patients (↑ PML)
 - Maintain high trough [IFX]
 - After 1 yr of complete mucosal healing, may consider stopping ATNF
- UC
 - May maintain with IFX + AZA, or AZA
 - Duration of continued ATNF unknown

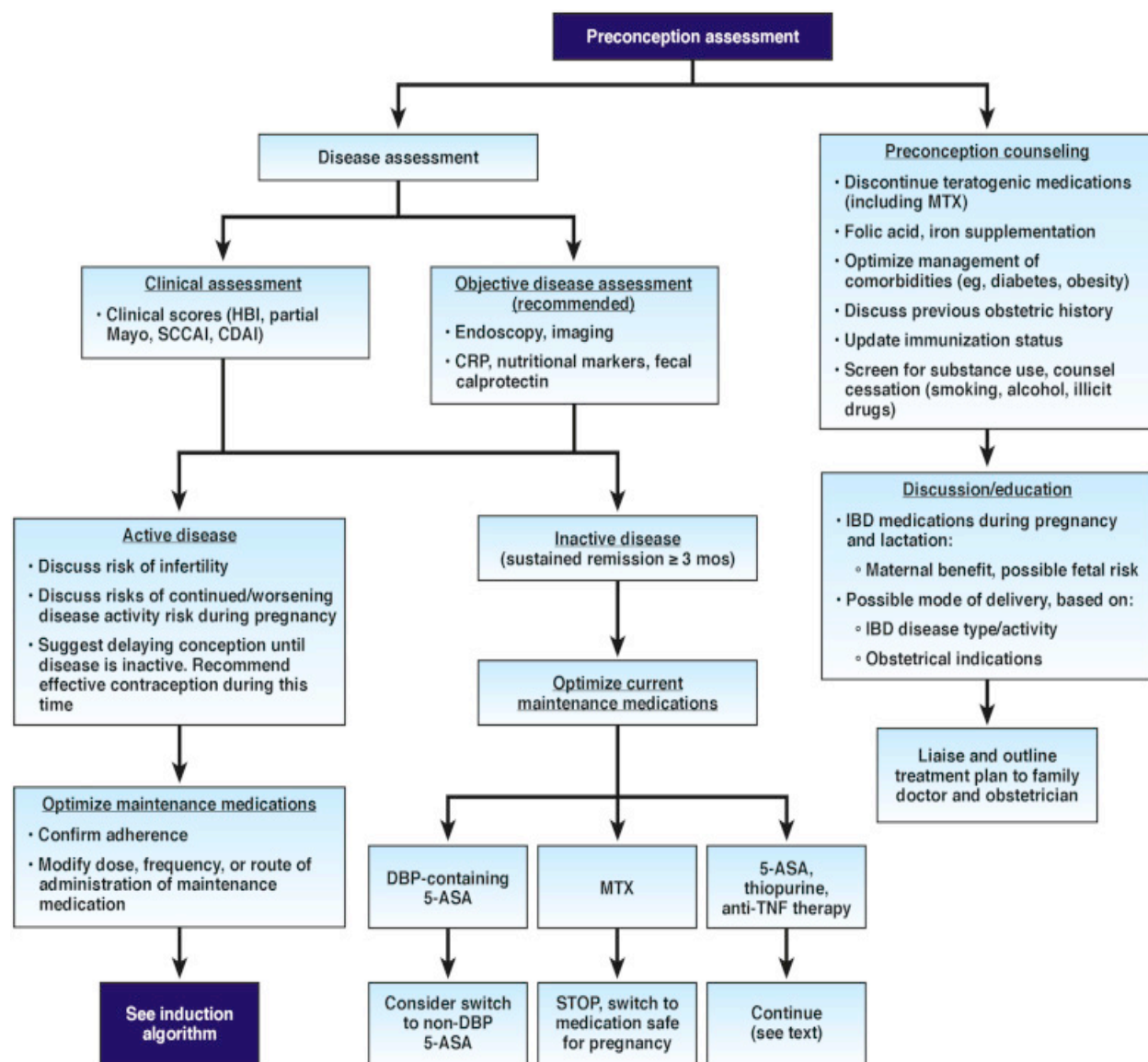
* Note: American Gastrointestinal Association (AGA) guidelines: “....make no recommendations for or against the combination of an anti-TNF- α drug and a thiopurine versus and an anti-TNF- α drug alone to maintain remission induced by a combination of these drugs in patients with CD” (ATNF + AZA → ATNF +/- AZA maintenance in CD) (Terdiman JP, et al. Gastroenterology 2013; 145: 1459-1463).

Abbreviations: ATNF, anti-tumour necrosis factor; AZA, azathioprine; CD, Crohn disease; Cs, corticosteroids; HBV, hepatitis B virus; HIV, human immunodeficiency virus infection; IBD, inflammatory bowel disease; IFX, infliximab; NMSC, non-melanoma skin cancer; PML, progressive multifocal leucoencephalopathy; TB, tuberculosis infection; UC, ulcerative colitis



Management of Inflammatory Bowel Disease in Pregnancy: Toronto Consensus Statements

Nguyen GC, et al. Gastroenterology 2016; 150: 734-757.



Abbreviations: CDAI, Crohn's Disease Activity Index; CRP, C-reactive protein; DBP, dibutyl phthalate; HBI, Harvey-Bradshaw Index; MTX, methotrexate; SCCAI, Simple Clinical Colitis Activity Index

Printed with permission: Nguyen GC, et al. Gastroenterology 2016; 150: 734-757, Figure 1.



❖ Preconception

- Recommend women of reproductive age with IBD receive preconception counselling to improve pregnancy outcomes
 - Women overestimate the risk of infertility associated with IBD
 - ↑ infertility with ileal pouch-anal anastomosis (RR of 3.91)
 - Rate of in vitro fertilization after IPAA comparable to those without IBD
- Recommend IBD to be managed by a gastroenterologist (GI) as well as high risk obstetrician (OB)
 - Frequency of follow up is individualized. Should be at least once.
- In women with IBD who are contemplating pregnancy
 - Recommend objective disease evaluation before conception to optimize disease management
 - Risks for prematurity, low birth weight, congenital abnormalities and C section delivery, VTE (more pronounced risk with active disease)
 - Achieve steroid free remission for at least 3 months before conception
 - Disease activity should be objectively assessed, according to recommendation for non-pregnant patients (mucosal healing)
 - Plan pregnancy for time when disease is inactive on colonoscopy
- In women with UC who are contemplating pregnancy and taking 5-ASA formulation containing dibutyl phthalate (DBP; Asacol, Mesasal)
 - Switch to 5-SAS without DBP
 - DBP helps with localized release of medication
 - ↑ risk of inhibit utero reproductive development → abnormal neurodevelopment
- Women with IBD taking Methotrexate
 - Stop 3 mon before attempts to conceive to minimize risk of teratogenicity
 - 3.4 fold ↑ risk in cardiovascular defects and 2.6 fold ↑ risk of oral cleft
 - If a woman becomes pregnant while taking MTX, immediately discontinue and refer for OB consultation

❖ During pregnancy

- In pregnant women with active / complicated IBD
 - Consult with high risk obstruction (OB)
 - ↑ risk of C section in active disease
 - Complicated features
 - Prior laparotomy
 - Prior colectomy with IPAA
 - Perianal disease
 - History of prior C section or adverse perinatal outcomes
 - Use of biologics or combination therapy: suggest a history of complicated disease
- In pregnant women who require hospitalization for IBD
 - Recommend transfer to tertiary care center with access to GI / OB
 - Prefer high risk OB



- Pregnant UC patients on po +/- pr 5-ASA maintenance continue throughout pregnancy
 - ↑ risk for relapse during pregnancy and postpartum period
 - Highest risk of relapse in first trimester (RR 8.80)
 - No ↑ risk of congenital abnormalities abortion or preterm delivery
 - Higher doses of sulfasalazine may ↓ absorption and ↓ serum concentrations of folic acid (give folic acid 2 mg/day for the pregnancy)
- Continue thiopurine throughout pregnancy
 - ↑ risk of preterm birth, but not congenital abnormalities
 - Altered metabolism of thiopurines during pregnancy
 - Measure 6-thioguanine nucleotide levels
- Continue anti-TNF maintenance during pregnancy: recommend continuation
 - In select pregnant patients with low risk for a relapse of IBD who have a compelling reason to discontinue anti-TNF therapy (ATNF) to minimize fetal exposure
 - Administer last dose at 22 to 24 weeks gestation
 - Low risk of relapse
 - Sustained symptomatic remission during 12 mon before conception
 - No active disease on endoscopy or imaging during preconception period
 - No prior secondary loss of response to anti-TNF or dose escalation
 - No prior intestinal resections, no hospitalizations in past 36 mon
 - Monoclonal antibodies are large and require active transport across the placenta, and this becomes most prominent in 3rd trimester
 - ATNF detected in infants up to 6 mon
 - Certolizumab has significantly less transfer
 - No significant increase in risk of congenital malformation, spontaneous abortion, infection in offspring
- In pregnant women with IBD on combination anti-TNF and thiopurine therapy
 - Switch to monotherapy (individualize)
 - No evidence of pregnancy-related complications
 - Possible infection at 12 mon of age
- In pregnant women with UC who have mild to moderate disease flare while on 5-ASA maintenance therapy
 - Optimized 5-ASA po / pr dose to induce symptomatic remission
- In pregnant women with CD who have perianal sepsis requiring antibiotic therapy
 - Metronidazole and / or ciprofloxacin
 - ↑ risk factor for intestinal-genitourinary fistulas and anorectal abscesses in pregnant CD
- Pregnant patients with IBD who have flare on optimal 5-ASA or thiopurine maintenance therapy
 - Systemic steroids or anti-TNF to induce remission
 - Inconsistent data about congenital malformation on steroids: possible cleft palate
 - Budesonide: high first pass metabolism and may be preferred in mild to moderate CD
 - Short acting prednisone, prednisolone, methylprednisolone are more efficiently metabolized and may result in lower fetal exposure



- In pregnant patients with IBD who have steroid-resistant flare
 - Anti-TNF therapy to induce remission
 - Little data on response to induction therapy
 - Early delivery may be preferable in those who are at least 37 weeks gestation
- Patients with IBD who are thiopurine naïve and starting anti-TNF
 - Anti-TNF monotherapy
 - ↑ risk of adverse reactions (e.g., pancreatitis)
- Pregnant patient hospitalized for IBD +/- C-section
 - Anticoagulant thromboprophylaxis (LMWH)
- Suspected IBD flare
 - Flexible sigmoidoscopy / colonoscopy if results will affect antenatal management
 - Defer to second trimester whenever possible
 - Sedation with meperidine or fentanyl
 - Possible oral cleft with benzodiazepines (avoid particularly in first trimester)
 - If sedation with fentanyl isn't adequate
 - Midazolam
- In IBD / suspected flare
 - Limiting radiological investigations to use sonography and MRI
- Urgent surgery should be performed regardless of trimester when patients with severe colitis are non-responsive to medical management.
- Base decision regarding C section on OB considerations and not diagnosis of IBD alone
 - Active / worsening perianal disease
 - Previous trauma to area
 - Short perianal length
- Pregnant women who have undergone IPAA
 - Consider C section
 - ↓ anal sphincter injury with OB and surgeon
- Those with CD and active perianal disease
 - C section
 - ↓ risk of perianal injury
 - Common for 4th degree tear

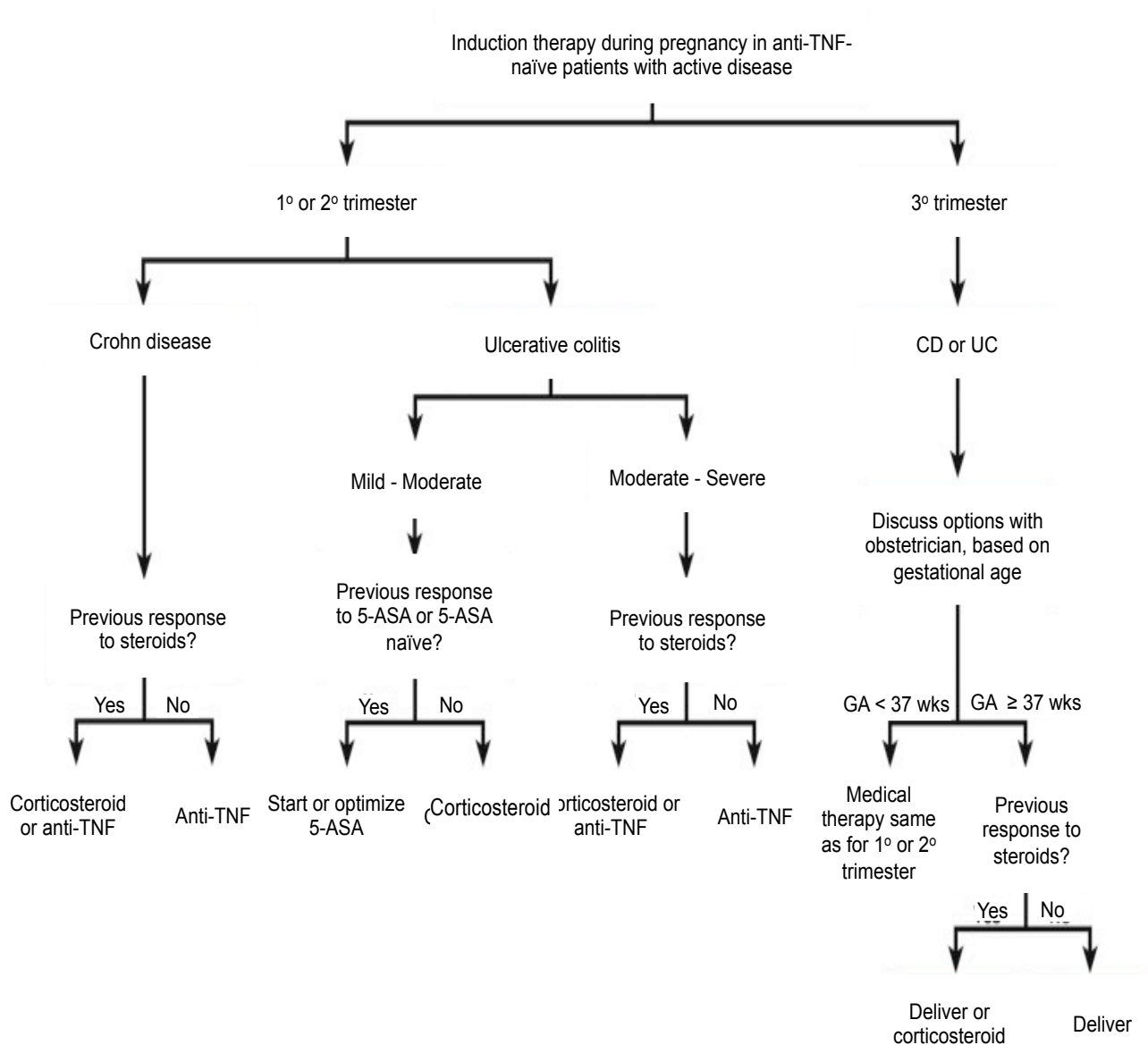
❖ Postpartum

- Decision to breastfeed should not be influenced by
 - No need to avoid 5-ASA, systemic steroids, thiopurine, anti-TNF therapy
 - Avoid breastfeeding on methotrexate
- For newborns of women who were on anti-TNF during pregnancy
 - Avoid live vaccines for first 6 mon



Algorithm for Induction Therapy in Pregnant Women with IBD: Toronto Consensus Statement

Nguyen GC, et al. Gastroenterology 2016; 150: 734-757.



* Individualized per existing clinical practice guidelines and, in the case of UC, according to disease severity.

† Generally, if GA is less than 37 weeks, the theoretical risk of induction therapy would be less than the risk of preterm delivery. GA, gestational age.

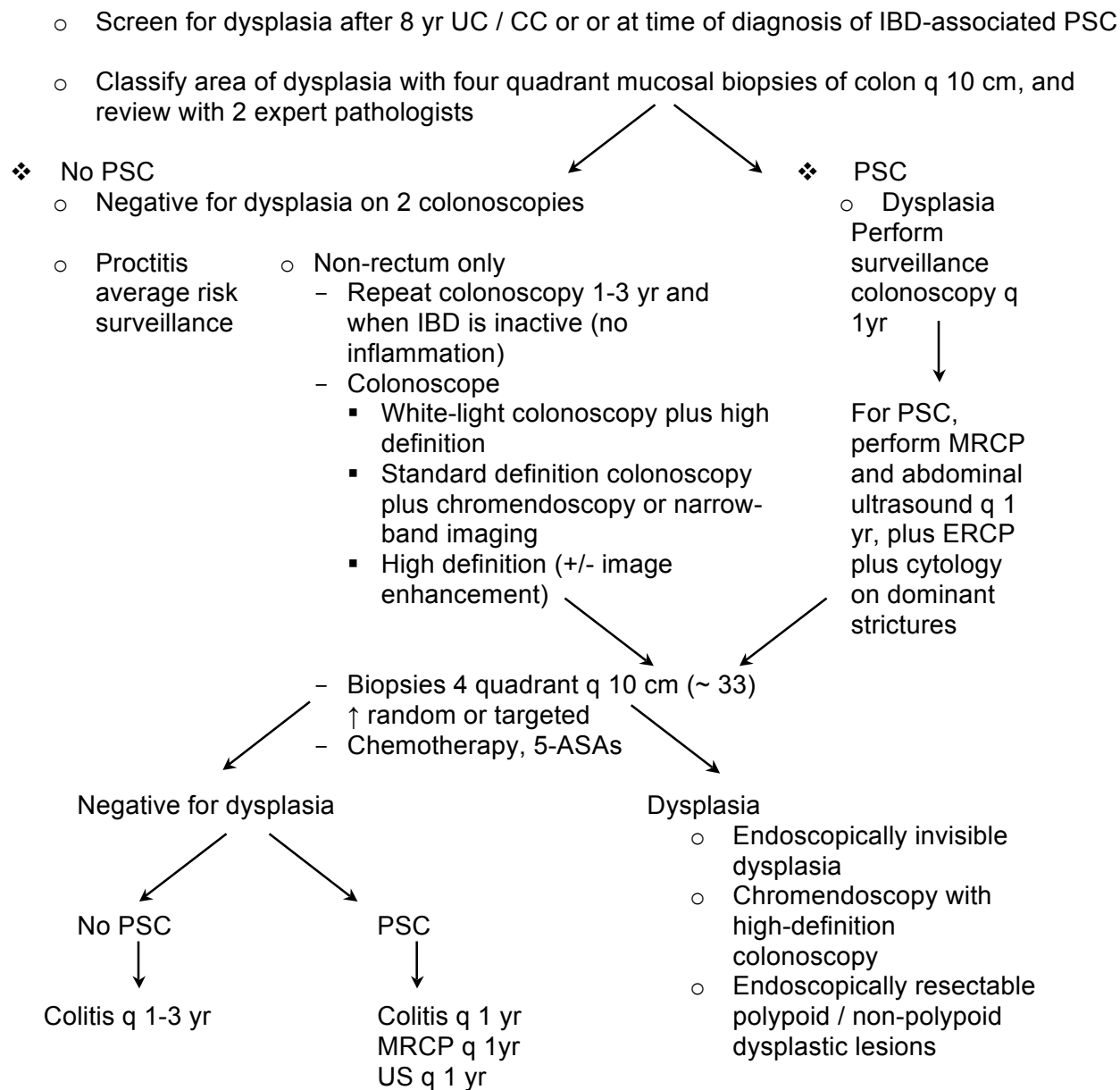
Printed with permission: Nguyen GC, et al. Gastroenterology 2016; 150: 734-757, Figure 2.



Diagnosis and Management of Colorectal Cancer (CRC) in Inflammatory Bowel Disease (IBD): AGA / ASGE Guidelines

Abbreviations: AGA, American Gastrointestinal Association; ASGE, American Society of Gastrointestinal Endoscopy

Farraye FA, et al. Gastroenterology 2010; 138: 738-745; and Laine L, et al. Gastrointestinal Endoscopy 2015; 81: 489-501.



Abbreviations: ASAs, aminosalicic acid; Col + bx, colonoscopy plus colonic mucosal biopsies; MRCP, magnetic residence cholangiopancreatogram; US, abdominal ultrasound



➤ Clarification

- The risk of developing CRC in ulcerative colitis (UC) is equivalent to the risk in Crohn colitis (CC), if the correction is made for duration and extent of the bowel inflammation.
- It is presumed that chronic recurrent colitis leads to dysplasia, which progresses to CRC; at present, dysplasia is the best marker we have for CRC development in IBD.
- When Crohn colitis involve > 1/3 of colon, risk of CRC is equivalent to duration-matched UC.

➤ Endoscopic

- Dysplasia may be flat, or elevated
 - Raised dysplasia is sometimes referred to as dysplasia-associated lesion or mass (DALM)
 - Adenoma-like DALMs are well-circumscribed, smooth / papillary, non-necrotic, sessile or pedunculated polyps, and if present outside of area of inflammation, are managed like sporadic and not IBD-related lesions
 - Non-adenoma-like DALMs are velvety patches, irregular bumps or nodules, broad-based masses or strictures which are associated with CRC in IBD (38% to 83%) and are treated by colectomy

➤ Histologically

- The Vienna classification of dysplasia has 5 diagnostic criteria, and is used widely in Europe and in Japan
- The Riddel classification has the nomenclature for dysplasia
 - Negative
 - Indefinite
 - Low grade (LGD)
 - High grade (HGD)
- The histological differences between these two classification systems is the inclusion in the Vienna of
 - 3 subgroups for HGD
 - High-grade adenoma / dysplasia
 - Non-invasive carcinoma (carcinoma in situ)
 - Suspicious of invasive carcinoma
 - 2 subgroups for adenocarcinoma
 - Intramucosal
 - Submucosal, or beyond

Note:

- Because American and Canadian trainees will be tested using the Simple Riddle classification, this classification system will be used here.
- Importantly, there are no clinically important differences in the two approaches.

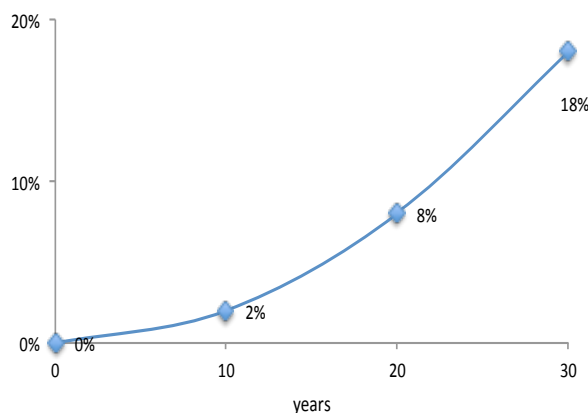


➤ Risk factors for CRC in IBD

Risk factors	Absolute	Relative (confidence interval)

❖ Patient

○ Duration



Overall ~ 2.8

○ Extent

- Rectum	1.7 (0.8 - 3.2)
- L-sided	2.8 (1.6 - 4.4)
- Pancolitis	14.8 (11.4 - 18.9)

○ Family history

- 1 st degree relative	
< 50 yr	2.5 (1.4 - 4.4)
> 50 yr	9.2 (3.7 - 23.0)

○ Age of onset of IBD

- < 15 yr	40%
- > 15 yr	25%

❖ Colon

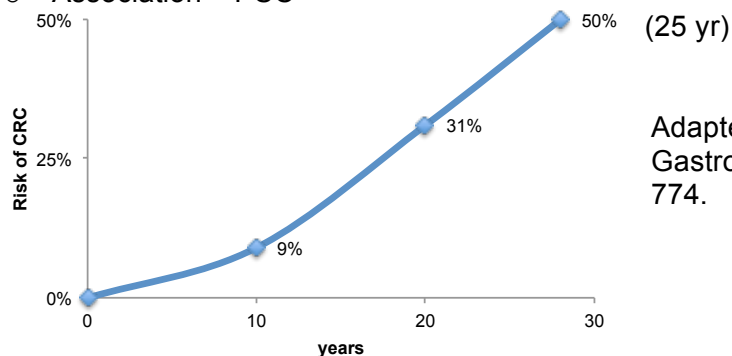
○ Inflammation demonstrated by

- Colonoscopy	5.1 (2.7 - 11.1)
- Histology	3.0 (1.4 - 6.3)

○ Complications

- Shortening	28.4 (1.6 - 512.2)
- Stricture	5.7 (1.7 - 18.9)
- Pseudopolyps	2.1 (1.2 - 3.7)

○ Association – PSC



Adapted from: Farraye FA, et al. Gastroenterology 2010; 138: 746-774.



Venothrombosis (VTE) in Inflammatory Bowel Disease (IBD): CAG Guidelines

Abbreviation: Canadian Association of Gastroenterology

Nguyen GC, et al. Gastroenterology 2014; 146: 835-48.

❖ Hospitalization (moderate / severe activity of IBD flare)

- Bleeding mild
 - Anticoagulant thromboprophylaxis
 - Low molecular weight heparin (LMWH), or
 - Unfractionated heparin (low-dose), or
 - Fondaparinux
- Bleeding severe
 - Mechanical thromboprophylaxis (preferably IPC)

↓ If bleeding becomes mild

 - Anticoagulant thromboprophylaxis (ACT)
- Non-IBD reasons for hospitalization, general surgery, major abdominal pelvic procedure
 - Anticoagulant thromboprophylaxis (ACT)

❖ Outpatients

- IBD flare (moderate / severe)
 - No previous VTE
 - No anticoagulation
 - No need to test for hypercoagulable state (inherited or acquired)
 - Previous VTE (not related to major surgery)
 - Anticoagulant thromboprophylaxis (ACT)
 - 1st VTE
 - Anticoagulant thromboprophylaxis

↓

For 3 mon after IBD flare
- No IBD flare
 - 1st VTE, IBD risk factor
 - Anticoagulant thromboprophylaxis (ACT)

↓

Long-term, periodic review
 - 1st VTE, IBD risk factor plus non-IBD related reversible provoking factor (RRPF)
 - Anticoagulant thromboprophylaxis (ACT)

↓

> 3 mon ACT, plus for at least 1 mon after non-IBD RRPF resolved
- Pregnancy
 - Cesarean section (regardless of VTE history)
 - Anticoagulant thromboprophylaxis (ACT)



❖ Splanchnic vein thrombosis (SVT)*, acute

- Symptomatic
 - IBD flare
 - Anticoagulation (ACT) for 3 mon after IBD flare resolved
 - No IBD flare, non-IBD RRPf
 - Anticoagulation (ACT) > 3 mon, plus
 - For at least 1 mon after non-IBD RRPf resolved
 - No IBD flare
 - No RRPf
 - Anticoagulation (ACT)
- ↓
- Long-term, periodic review
- Asymptomatic (incidental finding)
 - No anti-coagulation (ACT)

* portal, mesenteric, +/- splenic vein thrombosis

“Play a crucial role in finding your own
humility and humanity.”

Grandad



ENDOSCOPY IN PATIENTS WITH INFLAMMATORY BOWEL DISEASE (IBD): ASGE GUIDELINES

Abbreviation: ASGE, American Society for Gastrointestinal Endoscopy

Shergill AK, et al. Gastrointestinal Endoscopy 2015; 81: 1101-1121.

❖ Crohn Disease (CD)

- EGD
 - The yield of granulomas on biopsy of the upper GI is twice as high as in the colon (~50% vs ~25%)
 - For this reason EGD plus biopsy is recommended to be performed in children with suspected Crohn disease, as well as colonoscopy with biopsies
 - Lymphocytic gastritis is also commonly formed on EGD of the stomach in children with Crohn disease
- Capsule endoscopy (CE)
 - Sensitivity > 80%
 - Negative predictive value (NPV) > 96%
 - Diagnostic yield CE = MRE > SBFT / CTE
 - Change in medical therapy ~60%

Safety Alert

- Before performing a CE in the patient with Crohn disease
 - Potency capsule study
 - Diagnostic imaging study (e.g., MRE, CTE, SBFT)

Abbreviations: CD, Crohn disease; CE, capsule endoscopy; CTE, computerized tomographic enterography; EGD, esophagogastroduodenoscopy; MRE, magnetic resonance enterography; SBFT, small bowel follow through (barium)

❖ Enteroscopy

➤ Types

- Push enteroscopy (PE)
- Single or double balloon (SB, DB)

Enteroscopy	Yield, Overall	Yield, Active Inflammatory Disease	Adverse Events	Change in Clinical Management
- SB / DB	~40%		1%	
▪ Dilation	70%			
- DB	~60%	16%		~75%



❖ Endoscopic ultrasound (EUS)

- Give the performance characteristics for EUS, MRI and EUA for CD fistula detection and outlining fistula anatomy.

	EUS	MRI	EUA
○ Fistulae			
– Detection			
▪ Sensitivity	87%	87%	
▪ Specificity	43%	69%	
– Anatomy (accuracy)	91%	87%	91%
– ECCO consensus guidelines suggest that for investigation o perianal fistulae			
▪ Detection MRI			
▪ Follow-up medical / surgical therapy EUS**			

* Accuracy of 100% when using any 2 of these three choices

** This EUS follow-up of CD perianal fistulae with EUS may improve clinical outcomes

Abbreviations: ECCO, European Crohn's and Colitis Organization

While Crohn disease induces the terminal ileum in about 80% of patients, “background ileitis” occurs in about the same proportion off patients with pancolitis from UC. If the small bowel is involved with typical changes of CD, and there is colitis, it will be Crohn colitis, not UC.

- Give the features of terminal ileum, which favour the diagnosis of backwash ileitis versus Crohn ileitis.

Feature	Backwash (UC)	Crohn disease (CD)
○ Endoscopy		
– Short length	+	-
– Pancolitis	+	-
– Continuous colon to ileum involvement	+	-
– Complications: stricture, stenosis, ulceration	-	+
– Severity T1 > cecum	-	+
– Deep / serpiginous ulcers	-	+
– Cobblestone mucosa	-	+



Feature	Backwash (UC)	Crohn Disease (CD)
○ Histopathology		
– Mixed mild lamina propria inflammation	+	-
– Basal lymphoplasmacytosis	-	+
– Atrophy	-	+
– Crypt distortion	-	+
– Epithelial changes	-	+
– L-side colon pyloric gland and Paneth cell metaplasia	-	+
– Granulomas*		
▪ Epithelial	+	+
▪ Lamina propria	-	+

* Do not take mucosal biopsies from close to a resection staple line, since it may be have a granuloma or pseudogranuloma not related to the diagnosis of CD.

Endoscopy Alert

- When differentiating UC from CD, take multiple biopsies from endoscopically normal as well as abnormal areas.

➤ Disease activity scores

- Ulcerative colitis
- Pediatric Ulcerative Colitis Activity Index (PUCAI)
- Crohn disease
 - Simple endoscopic scoring system
 - Post-operative Rutgerts score
 - Capsule endoscopy

Source: www.giejournal.org

Issues with IBD Activity Scores

- No accepted standard
- Except for PUCAI, poor condition with symptoms
- No accepted definition for mucosal healing



Clinical Pearl

- Inflammation in the cecum (cecal “patch”) or around the orifice of the appendix (periappendiceal “patch”) is a curiosity, with no diagnostic, therapeutic or prognostic importance.

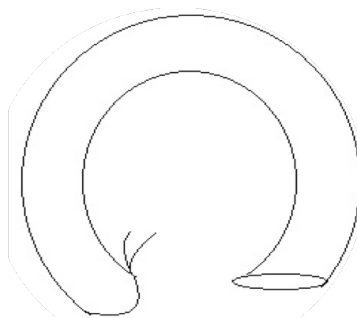
Screening and Surveillance for Colorectal Cancer (CRC) in IBD

- Average risk
- ↑ risk
 - Family history
 - Inherited CRC or polyposis
 - UC / Crohn colitis +/- PSC

❖ Screening Intervals

- The old
 - Many guidelines from a host of professional organizations (www.giejournal.org), generally recommend the initiation of surveillance for colorectal cancer (CRC) depends upon the site of the colitis, and the duration of the disease.

- Beyond L-side, start often 8-10 yr of IBD



- Left-sided disease
 - Start after 15 yr IBD
- Rectum proctitis as per non-IBD population

- Screening surveillance recommended for Crohn disease which induces $\geq 1/3$ of colon
- Consideration for earlier colonoscopy for ↑ risk IBD patients
- Endoscopic (white light) and biopsy (4-quadrant, 1 10 cm)

- The new
 - Begin colonoscopy before 8 yr disease, regardless of extent of disease
 - Take into account ↑ risk → colonoscopy q 1 yr
 - Associated primary sclerosing cholangitis (PSC)
 - Family (1st degree relative under 50 yr) / personal history of adenomatous polyps / CRC
 - Stricture (risk factor in UC but not CD)
 - Biopsy evidence of any grade of dysplasia in last 5 yr
 - Take biopsies 4-quadrant q 5 cm from L-side of colon



- Targeted biopsies e.g., chromendoscopy (methylene blue, indigo carmine) / high definition endoscopy
 - Non-polypoid Paris classification (2-3x ↑ dysplasia detection, NNT 14 rate)
 - Flat (II, depressions (IIc)
 - ↑ visibility of nodularity, elevation (IIa; < 2.5 mm above mucosa)
- Random plus targeted biopsies to bottom

Dollars Making Sense!

- The dead dinosaur
 - The “term” dysplasia-associated lesion or mass (DALM) has been replaced by the Paris Classification term “non-polypoid lesion”

In screening and surveillance for CRC in IBD justified?

- ↓ 5 yr
 - Mortality CRC-related from ~2.5% to zero!
 - Cost-effective
- Surgery → endoscopically
 - Invisible
 - Unsectable
 } Dysplasia
 - Ensure that biopsy margins are free of dysplasia

Dysplasia

➤ Useful Stats

- Detection of dysplasia as compared with white light
 - High resolution 9%
 - Chromendoscopy ~20%
- Colectomy
 - HGD
 - Endoscopically invisible
 - LGD
 - Multifocal
 - Sporadic adenoma with colitis-free margins
 - Polypectomy, followed by standard surveillance
 - Risk of synchronous or metachronous CRC with flat lesion not visible by white light (standard) colonoscopy
 - LGD ~ 20%
 - HGD ~35%
 - On this basis, it is now recommended that close endoscopic surveillance be performed after mucosa resection 1-6 mon, then q 1 yr from resection margin



Pouchitis

- After proctocolectomy plus ileal pouch anal anastomosis (IPAA) lesion develop later in pouch

Initial Histopathology	Subsequent Hazard Ratio (HR)
- No previous dysplasia / CRC	2%
- Dysplasia	3.8
- Colorectal cancer	24.7

Safe Rule of Thumb

- In UC, any stricture is potentially a CRC, and must be managed as such.

Benign Stricture in UC

- Clinical response in ~ 90%
 - Repeat dilations require in 50% at 5 yr
 - Surgery required in 25% within 5 yr
- Adverse events 5% in 5 yr, especially when stricture > 2 mm
- Self-expandable metal stent (SEMS)
 - Stent migration

Anal Fissure

- Generally speaking, surgical therapy (internal sphincterotomy) is preferred to medical (non-surgical therapy) including
 - Glycerol trinitrate
 - Calcium channel blockers
 - Corticosteroids
 - Botulinum toxin injection
- Surgical healing ~95%, with incontinence ~9%, as compared to healing of ~90% with botoxin, and 60% with calcium channel blocker



MICROSCOPIC COLITIS: AGAI GUIDELINES

Abbreviations: AGAI, American Gastroenterological Association Institute

Nguyen GC, et al. Gastroenterology 2016; 150: 734-757

➤ Demography

- Predilection for females ≥ 60 yr
- 2 subtypes: lymphocytic colitis (M = F), collagenous colitis (F > M)

➤ Causes / associations

- PPIs, NSAIDs
- Lansoprazole
- No association with $\uparrow$ mortality, CRC or need for surgery

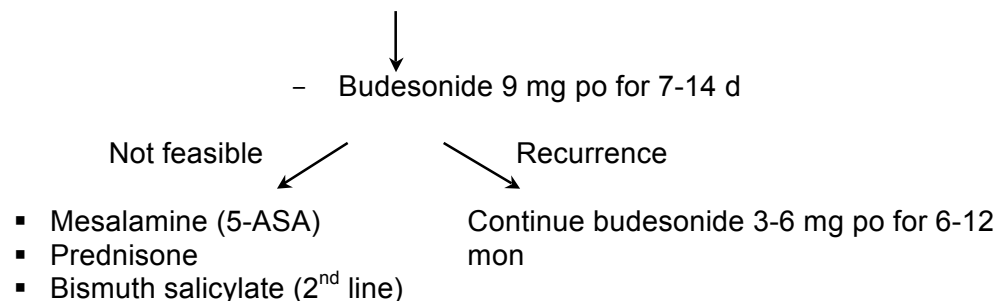
➤ Clinical

- Chronic lymphocytic or collagenous colitis watery diarrhea caused by microscopically but not endoscopically visible inflammation in the colon
- Diagnosed by colonic biopsy of normal-appearing mucosa from multiple segments

➤ Treatment

❖ Induction of clinical remission

- Chronic watery diarrhea, normal colonoscopy, but multiple mucosal biopsies positive for MC



❖ Maintenance of clinical remission

- For patients with recurrence of symptoms following discontinuation of induction therapy for microscopic colitis
 - Budesonide 6 mg po daily X 6 month, or
 - Budesonide 3 mg and 6 mg po alternating days X 12 months

Outside guidelines

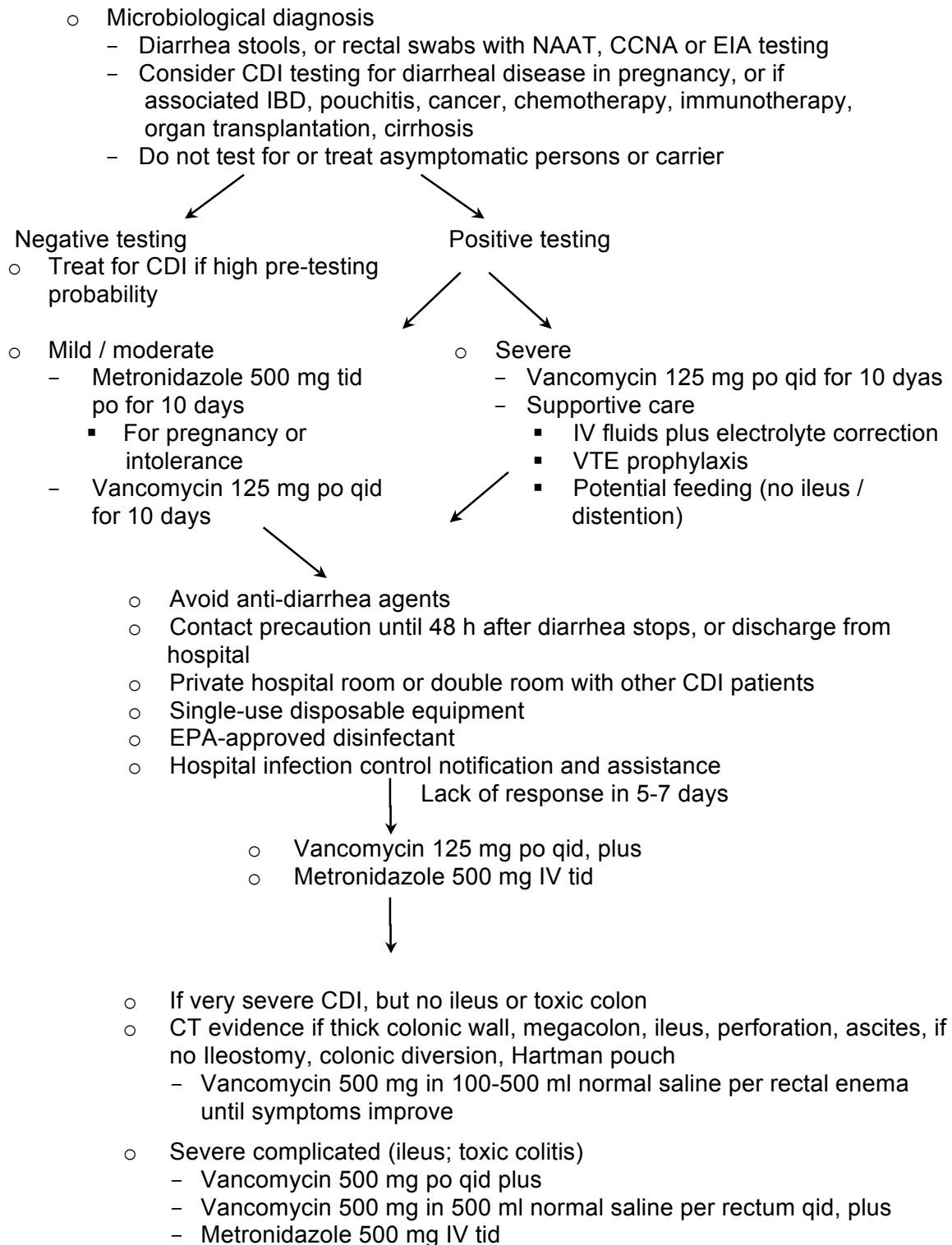
- Imodium 2 mg tid prn, if effective
 - In practice, may titrate budesonide to lowest effective dose
 - Consider cessation of maintenance after 6-12 months
 - Consider serology (tTG, tissue transglutaminase)
 - Consider osteoporosis screening and prevention (Dexa Scan for bone mineral density)

Abbreviations: AE, adverse effect; CRC, colorectal cancer; F, female; M, male; po, oral administration



CLOSTRIDIUM DIFFICILE INFECTIONS (CDI)

Surawicz CM, et al. Am J Gastroenterol 2013; 108: 478-498.



- Surgical consultation and subtotal colectomy with end-ileostomy if
 - Clinical
 - No improvement in 5 d
 - Level of consciousness (LOC; mental changes)
 - Organ failure
 - Laboratory
 - WBC > 50,000/ μ L
 - Lactate $\geq$ 5 mmol/L
- ↓
- Recurrent *C. difficile*
 - First recurrence
 - Repeat the initial regimen
 - CDI testing for IBD patients
 - Diarrhea flares
 - Pouchitis symptoms
 - Recent hospitalization or use of antibiotics
 - Continue IBD therapy but avoid if possible $\uparrow$ dose of immunosuppressants
 - Second recurrence
 - Vancomycin 125 mg po qid for 10 d, then 125 mg po od every 3 d for 10 times
 - Third recurrence
 - Fecal microbiota transplant (FMT)
 - Adjunct probiotics or IV immunoglobulin (IVIG) not recommended, except for IVIG in patient with hypogammaglobulinemia

Abbreviations: CCNA, *C. difficile* cytotoxic neutralization assay; EIA, enzyme immunoassay; EPA, Environmental Protection Agency; NAAT, nucleic acid amplification test; VTE, venothrombotic embolization

“Is there anyone so wise as to learn by the experience of others?”

Voltaire



ACUTE DIARRHEAL INFECTIONS IN IMMUNOCOMPETENT ADULTS (Not Including *Clostridium Difficile* Infection): ACG GUIDELINES

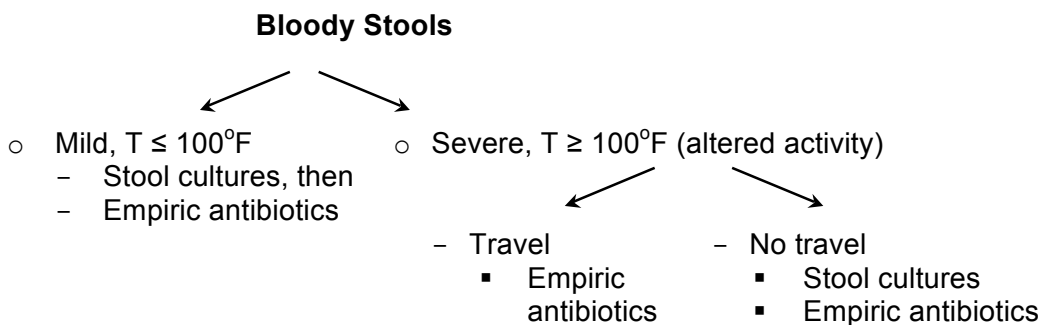
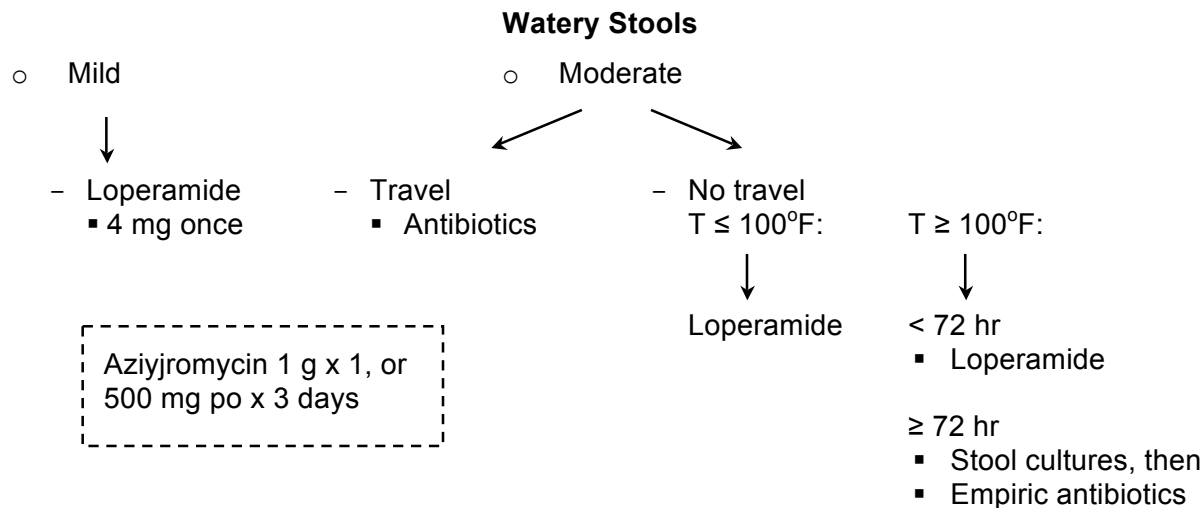
Abbreviation: ACG, American College of Gastroenterology

Riddles MS, et al. Am J Gastroenterol 2016; 111(5):602-22.

≥ 3 uniform stools in 24 hr, plus enteric symptoms



Oral replacement therapy (ORT), broths / soup, crackers, boiled / baked foods as tolerated



Aide de Memoire

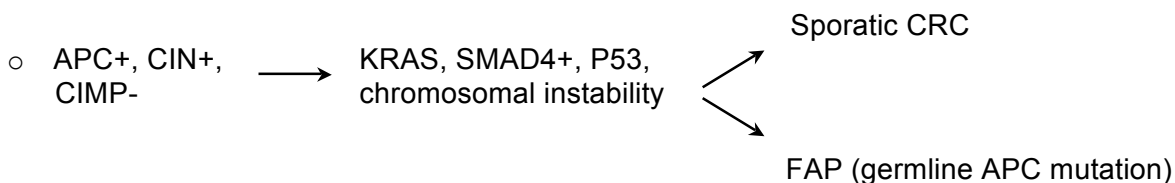
- Stool cultures
 - Watery diarrhea (moderate/severe) for ≥ 72 hr and no travel
 - Bloody diarrhea (mild or severe), no travel
 - Direct to empiric antibiotics
 - Watery diarrhea, moderate/severe, travel
 - Bloody diarrhea, severe, travel
- } Then to empiric antibiotics



COLORECTAL CANCER

Colorectal Cancer Genetics Made Easier

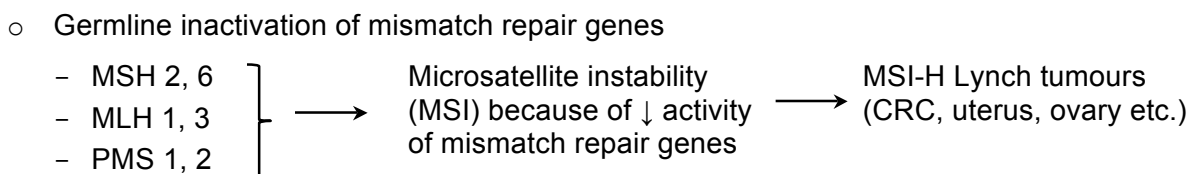
❖ Usual ("conventional") Pathway



- Note: Uncommonly the initial genetic abnormality in sporadic CRC is not mutation in APC but rather B-catenin or axin.

Abbreviations: APC, adenomatous polyposis coli; CIMP, CpG Island methylator phenotype; CIN, chromosomal instability; CRC, colorectal cancer; FAP, familial adenomatous polyposis

❖ Lynch (HNPCC) Microsatellite Instability Pathway



❖ Serrated pathway

Serrated Lesion	Mutations	Methylation	MSS / MSI-H / CIMP
○ TSA	→ - KRAS + - BRAF+	→ +/- abnormal methylation	→ MSS+, CIMP+/-
○ SSA (SSA / P)	→ - BRAF+	→ Abnormal methylation	→ MGMT, p16 → CIMP+, MSS+ → MLH1 → CIMP+, MSI-H



Colorectal Cancer Screening: US-MSTF Guidelines

Abbreviation: USMSTF, United States Multi-Society Task Force

Rex DX, et al. Am J Gastroenterol 2017; 112: 1016-1031.

➤ Choices of screening test

- Tier 1
 - Colonoscopy q 10 yr
 - FIT q 1 yr
- ↓
- Tier 2
 - CTC q 5 yr
 - FIT-fecal DNA q3yr
 - Flexible sigmoidoscopy q 5-10yr
- ↓
- Tier 3
 - Capsule colonoscopy q 5 yr

Abbreviations: CTC, CT colonography; FIT, fecal immunochemical test

Demonstration of Performance for Acceptable Quality Screening Colonoscopy

- Adenomas detection rate
 - Male $\geq 30\%$
 - Females $\geq 20\%$
- Cecal intubation rate $\geq 90\%$
- Split-dose bowel preparation
- Documentation
 - Quality of bowel preparation
 - Intubation / photography of
 - Ileocecal valve / terminal ileum
 - Appendiceal orifice

➤ Screening

Risk	Initiation of Screening	Frequency of Surveillance
○ Average risk		
- African American	45 yr	
- Non-African American	50 yr	
○ Risk family history		
< 60	- One 1st degree relative < 60 - Two 2nd degree relatives (with CRC) < 60	▪ 10 yr before age of diagnosis in youngest ▪ 1st-degree relative, or ▪ Age 40, whichever is earlier
≥ 60	- One 1 st degree relative ≥ 60 with CRC or advanced adenoma, SSA / TSA	Age 40

➤ Stopping Surveillance

- Prior screening
 - Up-to-date (colonoscopy, FIT) is negative
 - No prior screening
- } Stop screening colonoscopy age 75, or when life expectancy < 10 yr

Editors Suggestion: Maintain quality indicators for colonoscopy

○ Quantitative - Cecal intubation rate - Adenoma detection rate - Withdrawal time - Use of recommended surveillance	○ Qualitative - Record of explanation/consent - Bowel preparation - Patient comfort



Colonoscopy Surveillance after Normal Colonoscopy or after Screening Polypectomy: US-MSTF Guidelines – American and British Perspective

Abbreviation: USMSTF, United States Multi-Society Task Force

➤ Definition

○ High risk adenoma (HRA)	Low risk adenoma (LRA)
≥ 3 adenomas	1-2 tubular adenomas < 10 mm
≥ 1 tubular adenoma ≥ 10 mm	
≥ 1 villous adenoma	
○ High risk SSA	Low risk SSA
> 10 mm	< 10 mm
Any size with cytological dysplasia	No cytological dysplasia

➤ Background

- Interval adenomas or cancer occur between the baseline screening colonoscopy (“clearing colonoscopy”) and the appropriate-for-risk interval for the surveillance colonoscopy (metachronous lesions)
- There is a risk of developing interval CRC after polypectomy, or negative findings on baseline normal colonoscopy
 - Important lesions may be missed or not completely removed at baseline colonoscopy
 - Interval CRB may be located in the proximal colon, have microsatellite (MSI, and have CpG island methylator phenotype (CIMP), with accelerated tumour growth
 - The screening procedure may not have been a high quality colonoscopy

➤ Baseline colonoscopy

	Next Examination (interval)
○ No adenomas / polyps	10 yr
○ 3-10 adenomas*	3 yr
○ Distal HP < 10 mm	10 yr
≥ 1 tubular adenoma ≥ 10 mm*	3 yr
≥ 1 villous adenoma, any size	3 yr
≥ 1 adenoma with HGD	3 yr
> 10 adenomas	< 3yr

* The guidelines of the British Society of Gastroenterology (Airns SR, et al. Gut 2010; 59: 666-690) consider these to be HRA and recommend that the next surveillance colonoscopy be at 1 yr



> 5 small adenomas, or
 ≥ 3 adenomas, at least one ≥ 10 mm

No adenomas, but

- Sessile serrated polyps (SSP)
 - < 10 mm, no dysplasia } 5 yr
 - ≥ 10 mm } 3 yr
 - SSP with dysplasia } q 1 yr
 - TSA
 - SPS

Abbreviations: HGD, high-grade dysplasia; HP, hyperplastic polyp; HRA, high risk adenoma; LRA, low risk adenoma; SPS, serrated polyposis syndrome; SSP, sessile serrated polyp; TSA, traditional serrated adenoma

➤ Continued surveillance after the first follow-up colonoscopy

- Concept classify adenomas into high risk or low risk (HRA, LRA) for purposes of selecting interval for continued surveillance after the first follow-up colonoscopy (**not** initial screening colonoscopy)

➤ Guidelines

Baseline	Colonoscopy First Surveillance	Interval for Next (second) Surveillance Colonoscopy, yr
○ LRA	No adenoma	10
	LRA	5
	HRA	3
○ HRA	HRA	3
	LRA	5
	No adenoma	? (5 yr)
○ LRA	No adenoma(10) LRA (5) HRA (3)	○ HRA No adenoma (? 5 yr) LRA (5) HRA (3)

Cautionary Tips

- The goal of adequate bowel preparation is to detect lesions 5 mm; if the bowel preparation was poor, repeat the colonoscopy within 1 yr
- If new lower GI symptoms develop during the surveillance interval (3-5 yr), make decision to reinvestigate (earlier than next schedule surveillance colonoscopy) on a case-by-case basis, but erring on the side of caution

Source: Lieberman DA, et al. Gastroenterology 2012; 143: 844-857.



Optimizing Adequacy of Bowel Cleansing for Colonoscopy: US-MSTF / ASGE Guidelines

Abbreviations: ASGE, American Society of Gastrointestinal Endoscopy; US-MSTF, United States Multi-Society Task Force on Colorectal Cancer

- Perform high-quality colonoscopy after adequate bowel cleansing strategies
 - Repeat colonoscopy in ≤ 1 yr if preparation inadequate
 - Routinely assess and record adequacy of bowel preparation such as Ottawa Bowel Preparation scale
 - Adequate cleansing should be achieved in $\geq 80\%$
 - Preferably use split dose cleaning preparation (e.g., 4 L PEG-ELS formulation) with full fluids or low residue diet until the evening of the day before colonoscopy
- Cleaning preparation
 - Avoid sodium phosphate preparation in those elderly, as well as in children < 12 yr, those with IBD
 - High-volume preparations to be taken over longer period, or small-volume preparations over usual time interval
 - Pregnancy
 - Use additional purgatives for those persons with $\uparrow$ risk of inadequate preparation e.g.,
 - Spinal cord injury
 - Diabetes
 - Constipating medications
 - Previous colon resection
- If poor preparation consider
 - Through-the-scope enemas
 - Waking patient, continue purgation, and repeat same-day procedure

Bowel Prep Name	Points	Description
○ Ottawa Bowel Prep Scale rating for each colon segment [†]	4	– Inadequate (solid stool not cleared with washing and suctioning)
	3	– Poor (necessary to wash and suction to obtain a reasonable view)
	2	– Fair (necessary to suction liquid to adequately view segment)
	1	– Good (minimal turbid fluid in segment)
	0	– Excellent (mucosal detail clearly visible)
○ Ottawa Bowel Preparation Scale rating for the amount of fluid in the whole colon [†]	2	– Large amount of fluid
	1	– Moderate amount of fluid
	0	– Small amount of fluid

[†]Ottawa Bowel Preparation Scale total score is calculated by adding the scores of the right, transverse / descending, and sigmoid / rectum colon segments and the score for the fluid in the whole colon. The total Ottawa Bowel Preparation Scale score ranges from 14 (very poor) to 0 (excellent).

Abbreviations: PEG-ELS, polyethylene glycol-electrolyte lavage solution

Johnson DA, et al. Gastroenterol 2014; 109, 1528-1545; and Saltzman JR, et al. Gastrointestinal Endoscopy 2015; 81: 781-794.



Quality Measures for an Acceptable Colorectal Cancer Screening and Surveillance Program: AGAI Guidelines

Abbreviation: AGAI, American Gastroenterology Association Institute

Fayad NF and Kahi CJ. Clin Gastroenterol Hepatol 2014; 12: 1973-1980.

- Cecal intubation rates
 - Screening colonoscopy in healthy adults $\geq 95\%$
 - Non-screening $\geq 90\%$
- Adenoma detection rates (ADR)
 - Men $\geq 25\%$
 - Women $\geq 15\%$
- Proximal serrated polyp detection rate (PSP-DR) 5%

Note:

- ADR is the proportion of screening colonoscopies where ≥ 1 adenoma (proven by histopathology) is formed; ADR is considered the "... prime colonoscopy quality metric and is a proxy for a thorough examination of the colon."
- Other useful measures included overall polypectomy rate, adequacy of bowel preparation and sedation, colonoscopy withdrawal time, comfort of patient during examination, deaimented and complete informed consent including miss rate of polyps and risks od polypectomy, and indication for the procedure.

"Let's change the interactions between alerting,
orienting and executive functions, and control in a
standard curing paradigm."

Grandad



Fecal Immune Testing for Colorectal Cancer: ASGE, ACG, AGAI, and US-MSTF Consensus Statement

Abbreviation: ASGE, American Society for Gastrointestinal Endoscopy; ACG, American College of Gastroenterology; AGAI, American Gastrointestinal Association Institute; US-MSTF, United States Multi-Society Task Force on Colorectal Cancer

Robertson DJ, et al. Gastrointestinal Endoscopy 2017; 85: 2-21.

“Fecal immune testing (FIT) now is recognized as an important component of any CRC screening program.”

➤ The Task Force suggests

- One sample annual FIT testing for CRC using a quantitative FIT test with a lower threshold cut-off of $\leq 20 \mu\text{g/g}$ to define a positive test.
 - Use spontaneously passed stool
 - No need to alter diet or medications
 - No need to alter distribution mailing of FIT in warm climate



- When FIT is positive, perform a quality colonoscopy, even if the patient had a recent colonoscopy and it is before the scheduled examination.



- Do not perform EGD unless clinical features suggestive of upper GI pathology



- Consider repeat colonoscopy, depending on patient characteristics / risk.

➤ Target quality metrics to ensure quality assurance practices

- Completion rate $\geq 60\%$ (of those offered testing) (only 30% in Ontario)
- FIT test returned by laboratory
 - Unable to process $< 5\%$
- FIT +
 - Colonoscopy completed in persons FIT+ $\geq 80\%$ (only 75% in Ontario)
 - Adenoma detection rate
 - Males $> 45\%$
 - Females $> 35\%$

Abbreviation: EGD, esophagogastroduodenoscopy



Supportive Evidence

❖ Performance characteristics (average risk population)

Test for CRC	Sensitivity	Specificity	PPV
○ FIT			
– CRC	74 - 79%	94 - 96%	2.9 - 7.8
– AN			33.9 - 54

- “A positive FIT test
 - ↑ yield of colonoscopy
 - When FIT+, perform colonoscopy, not repeat FIT testing

➤ Need for repeat FIT testing at same testing period

- In asymptomatic, average-risk persons, the pooled performance characteristics of FIT for CRC are similar regardless of the number of FIT samples used
- To ↑ adenoma detection rate (ADR), repeat FIT applications

❖ Comparison of FIT testing at same testing period

- gFOBT vs FIT
 - Annual gFOBT → ↓ CRC-related mortality by 33%
 - FIT is superior to gFOBT for
 - CRC (RR, 1.96; 95% CI, 1.2 - 3.2)
 - AN (RR, 2.28; 95% CI, 1.68 - 3.10)

Test	SENS	SPEC	Adherence / Participation
– FIT	73%	> 95%	FIT > gFOBT by 20%
– gFOBT	33%	> 95%	RR, 1.16; 95% CI, 1.08 - 1.30

- Fecal DNA / multi-targeted test vs FIT

Test	SENS	SPEC	Adherence / Participation
– FIT	74% (24%)	95%	Values in brackets refer to findings for AN
– DNA	92% (42%)	87%	FIT is not effective to detect sessile serrated adenomas (SSAs)

- Flexible sigmoidoscopy (FS) vs FIT
 - Detection
 - CRC FS = FIT
 - AN FS > FIT

- Colonoscopy (Col) vs FIT
 - CRC Col = FIT
 - AN Col > FIT (1.9% vs 0.9%)

FIT > Col, 34% vs 25%
RR, 0.67; 95% CI, 0.56 - 0.80

- Recommendation (strong) to use FIT rather than gFOBT



❖ Interval for FIT

- Cost-effectiveness analysis
 - FIT q 1 yr = colonoscopy q 10 yr for life-years gained
- Recommendation
 - 1 sample annual FIT screening

❖ When FIT is positive

→ Colonoscopy

- High positive predictive value for CRC (2.9 - 7.8) and for AN (33.9 - 54)

→ CT colonoscopy (adenomas $\geq$ 60 mm)

SENS 89%; 95% CI, 84 - 92%

SPEC 75.4%; 95% CI, 59 - 87%

→ CT colonoscopy plus colon capsule endoscopy (CCE)

SENS 95%

SPEC 65%

Note: CCE completely
examined colon in only 73%

MCQ TRICK

- Give why FIT or gFOBT evaluates chronic lower but not upper GI bleeding.
 - Hemoglobin is degraded as it moves through the GI tract, so FIT/gFOBT are more likely to be positive with lower than with upper bleeding.
 - When a barium meal is performed to diagnose gastric cancer, the dilation rate by diagnostic imaging is not affected by whether the FIT is positive or negative.

Abbreviations: AN, advanced neoplasia; CI, confidential interval; gFOBT, guaiac fecal occult blood test; PPV, positive predictive value; RR, relative risk



Hereditary Gastrointestinal Cancer Syndromes: ACG, AGAI, US-MSTF and US-NCCN Guidelines

Abbreviation: ACG, American College of Gastroenterology; AGAI, American Gastrointestinal Association Institute; US-NCCN, United States National Comprehensive Cancer Network; US-MSTF, United States Multi-Society Task Force on Colorectal Cancer

Giardiello FM, et al. Am J Gastroenterol 2014; 109: 1159-1179; Ladabaum U, et al. Gastroenterology 2015; 149: 783-813; Rubenstein JH, et al. Gastroenterology 2015; 149: 777-782; Syngal S, et al. Am J Gastroenterol 2015; 110: 223-262.

- Consideration
 - Colon
 - Lynch syndrome (LS)
 - Familial adenomatous polyposis (FAP) and
 - MUTYH-associated polyposis (attenuated polyposis) or MUTYH-associated polyposis [MAP]
 - Peutz-Jeghers syndrome (PLS)
 - Juvenile polyposis syndrome (JPS)
 - Cowden syndrome (aka PTEN Hamartoma tumour syndrome)
 - Serrated / hyperplastic polyposis syndrome
 - Stomach
 - Hereditary diffuse gastric cancer (HDGC)
 - Pancreas
 - Hereditary pancreatic cancer

➤ Cumulative risks

- Give the cumulative risks of colorectal cancer in hereditary colorectal cancer syndrome.

Syndrome	Gene	Risk	Average Age of Diagnosis (yr)
○ Sporadic colorectal cancer		4.8%	69
○ Lynch syndrome	<i>MLH1</i> / <i>MSH2</i>	M: 27-74% F: 22-61%	27-60
	<i>MSH6</i>	M: 22-69% F: 10-30% M / F: 12%	50-63
	<i>PMS2</i>	M: 20% F: 15%	47-66
○ FAP	<i>APC</i>	100%	38-41
- Attenuated FAP	<i>APC</i>	69%	54-58
- <i>MUTYH</i> -associated polyposis	<i>MUTYH</i>	43-100%	48-50
○ Juvenile polyposis	<i>SMAD4</i> <i>BMPR1A</i>	38-68%	34-44
○ Peutz-Jeghers syndrome	<i>STK11</i>	39%	42-46
○ Cowden syndrome	<i>PTEN</i>	9-16%	44-48
○ Serrated polyposis syndrome	Not known	~>50%	48

Abbreviations: F, female; FAP, Familial adenomatous polyposis; M, male

Printed with permission: Syngal S, et al. Am J Gastroenterol 2015; 110: 223-262.



Familial Adenomatous Polyposis (FAP), Attenuated Familial Adenomatous Polyposis (AFAP) and MUTYH-associated polyposis (MAP)

- At risk or affected
 - Colonoscopy or sigmoidoscopy
 - At puberty, then q 1 yr
-
- Infants until 7 yr (q 1 yr)
 - A-fetoprotein
 - Ultrasound
- ↙ ↘
- Early total or subtotal colectomy
 - ↑ number of adenomas
 - Multiple adenomas > 6 mm
 - Multiple diminutive polyps
- EGD
 - Begin at 25-30 yr
 - Repeat q 6 mon to q 4 yr depending upon Spigelman stage of duodenal polyposis
- +
- Subtotal colectomy, or total colectomy with ileoanal pouch (IAP)
 - Post-surgical proctoscopy / pouchoscopy q 1 yr and ileostomy endoscopy q 2 yr
- Thyroid screening q 1 yr

Note: Even after colectomy for colonic FAP, the patient is at high risk of having perianal FAP, and annual EGD and biopsies must be performed.

“A mind that is stretched by a new experience
can never go back to its old dimensions.”

Oliver Wendell Holmes Jr



Lynch Syndrome (LS)

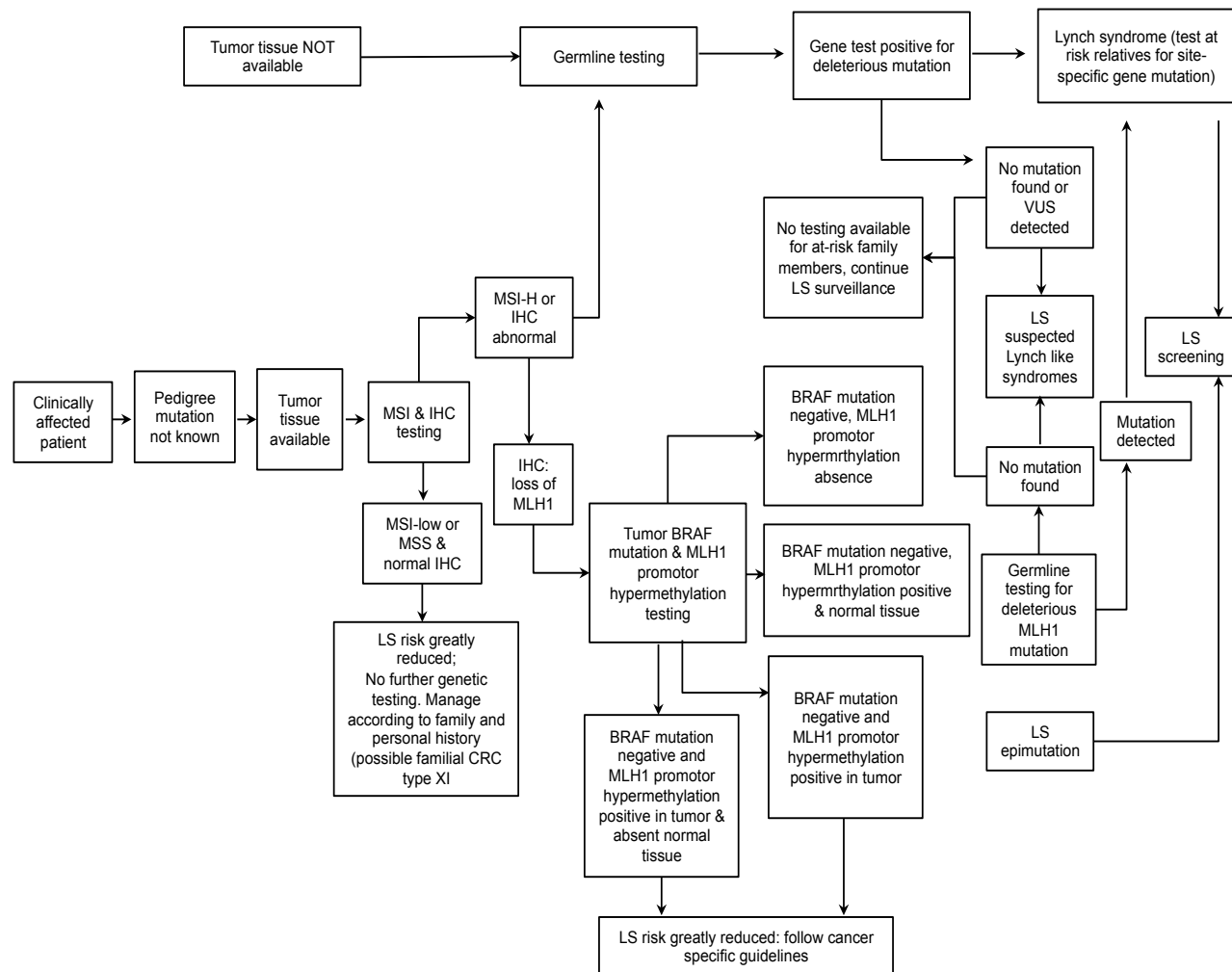
- Note
 - Also known as hereditary non-opolypsis colorectal cancer (HNPCC)

Abbreviation: USMSTF, United States Multi-Society Task Force

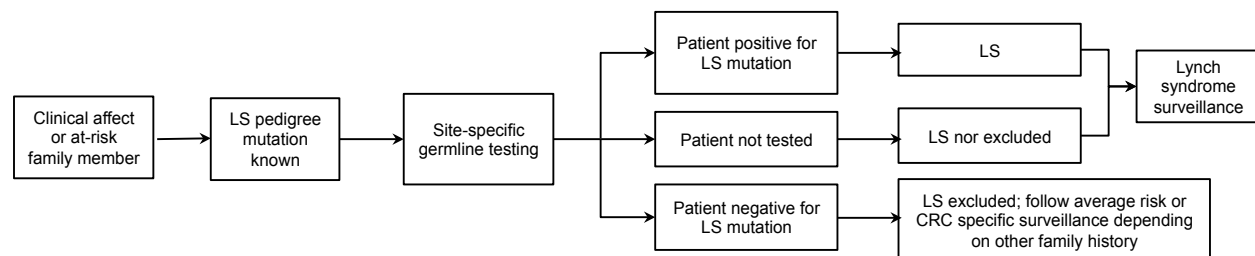
Giardiello FM, et al. Am J Gastroenterol 2014; 109: 1159-79.

➤ Traditional testing strategy

- When patient is clinically affected and the family mutation is unknown.



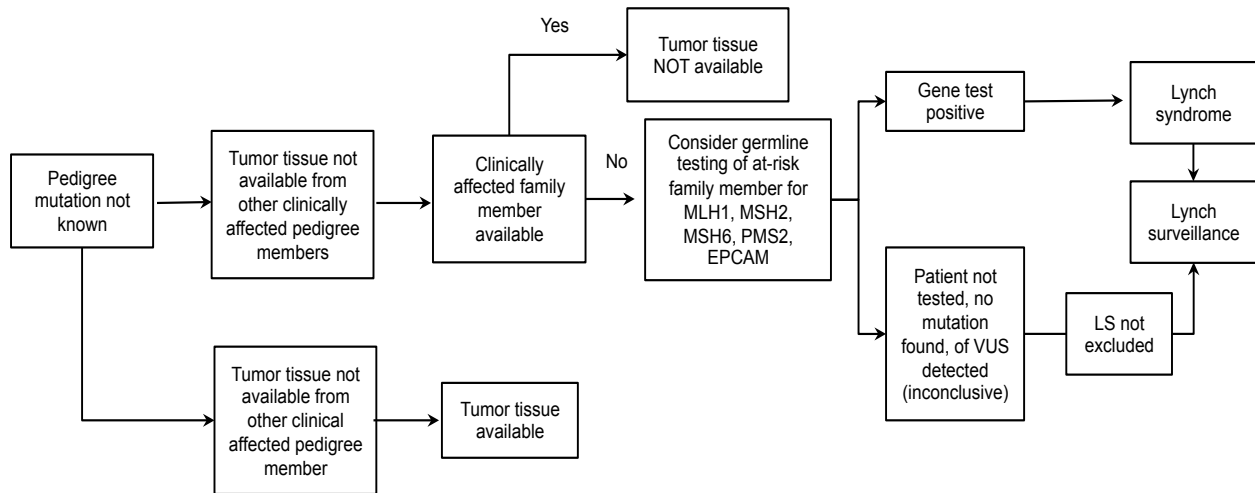
- When family mutation is known.



Printed with permission: Giardiello FM, et al. Am J Gastroenterol 2014; 109: 1159-79.

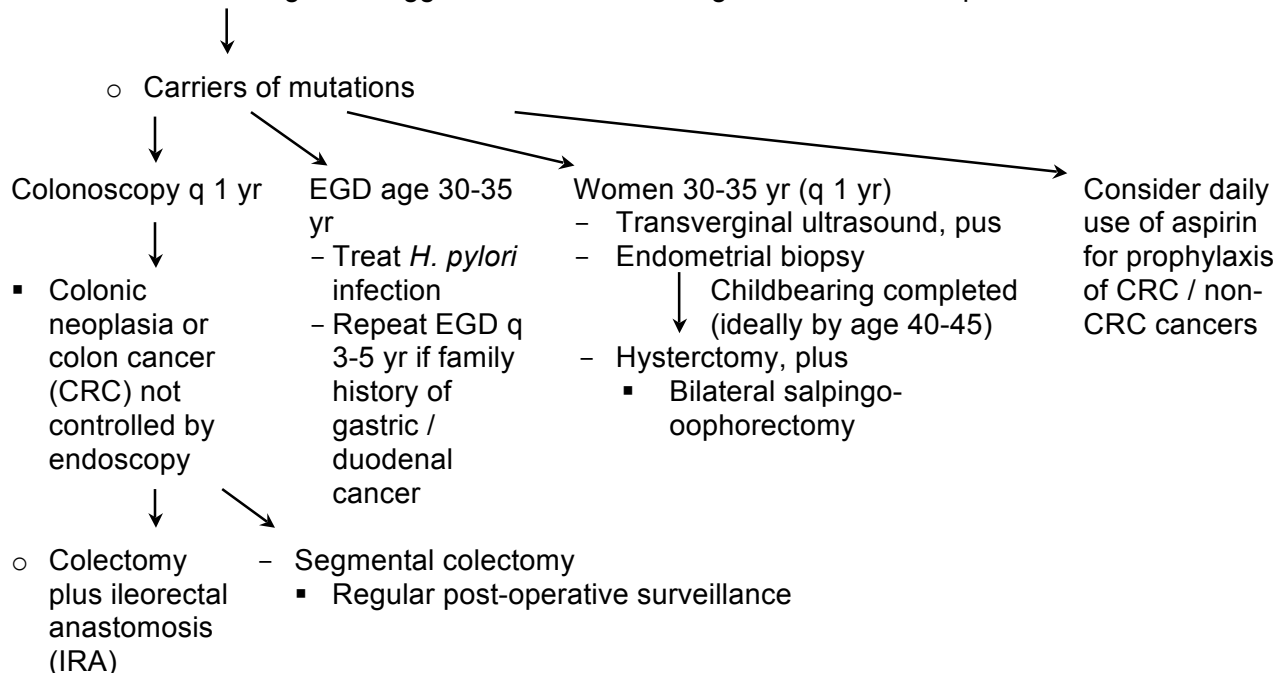


- At-risk family member when family mutation is not known.



Printed with permission: Giardiello FM, et al. Am J Gastroenterol 2014; 109: 1159-79.

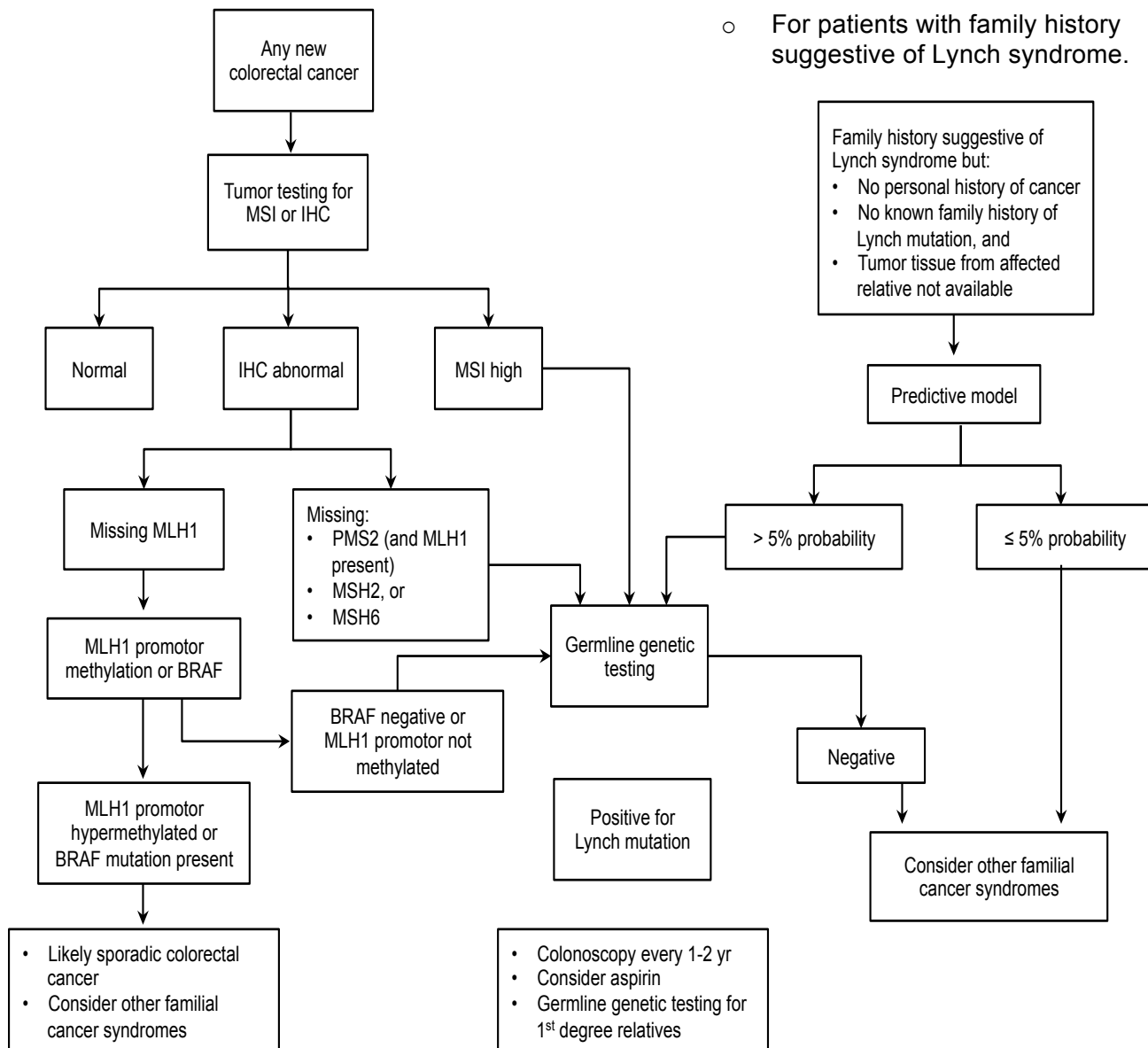
- Persons at risk for or affected by LS
 - Amsterdam criteria I / II, or revised Bethesda criteria
 - All persons with CRC risk $\geq 5\%$
 - Tumours showing deficiency of mismatch repair genes
 - Family mutation of LS proteins demonstrated on IHC showing microsatellite instability
 - MLH1 $\rightarrow$ plus BRAF testing, or MLH1 promoter hypermethylation
 - MSH2
 - MSH6
 - PMS2
 - EPCAM
 - VSH2
 - Other genes suggested from IHC testing of LS-associated proteins



➤ Clinical Decision Support Tool

Rubenstein JH, et al. Gastroenterology 2015; 149: 777-782.

○ Newly diagnosed colorectal cancer



Abbreviations: CRC, colorectal cancer; EGD, esophagogastroduodenoscopy; IHC, immunohistochemical (testing for LS-associated proteins; IRA, ileorectal anastomosis; LS, Lynch syndrome; US-NCCN, United States National Comprehensive Cancer Network

National Comprehensive Cancer Network, http://www.nccn.org/professionals/physicians_gls/f-guidelines.asp



Amsterdam criteria, revised Bethesda guidelines, and colorectal cancer risk assessment tool

❖ Physician Assessment of Risk of LS

○ *Amsterdam criteria*

- At least three relatives with colorectal cancer (CRC); all of the following criteria should be present:
 - One should be a first-degree relative of the other two;
 - At least two successive generations must be affected;
 - At least one of the relatives with CRC must have received the diagnosis before the age of 50 years;
 - Familial adenomatous polyposis should be excluded;
 - Tumours should be verified by pathologic examination.

○ *Amsterdam criteria II*

- At least three relatives must have a cancer associated with Lynch syndrome (colorectal, cancer of the endometrium, small bowel, ureter, or renal–pelvis); all of the following criteria should be present:
 - One must be a first-degree relative of the other two;
 - At least two successive generations must be affected;
 - At least one relative with cancer associated with Lynch syndrome (LS) should be diagnosed before age 50;
 - Familial adenomatous polyposis should be excluded in the CRC case(s) (if any);
 - Tumours should be verified whenever possible.

○ *Revised Bethesda guidelines*

- Tumours from individuals should be tested for microsatellite instability (MSI) in the following situations:
 - CRC diagnosed in a patient who is younger than 50 years of age
 - Presence of synchronous, or metachronous, colorectal or other LS-related tumours^a, regardless of age
 - CRC with MSI-high histology^b diagnosed in a patient who is younger than 60 years of age
 - CRC diagnosed in a patient with one or more first-degree relatives with an LS-related cancer, with one of the cancers being diagnosed under age 50 years
 - CRC diagnosed in a patient with two or more first- or second-degree relatives with LS-related cancer regardless of age



○ *Patient Input: Colorectal Cancer Risk Assessment Tool^c*

(Patient who answers yes to any question should have more comprehensive family history evaluation)

1. Do you have a first-degree relative (mother, father, brother, sister, or child) with any of the following conditions diagnosed before age 50?
 - Colon or rectal cancer
 - Cancer of the uterus, ovary, stomach, small intestine, urinary tract (kidney, ureter, bladder), bile ducts, pancreas, or brain
2. Have you had any of the following conditions diagnosed before age 50 years?
 - Colon or rectal cancer
 - Colon or rectal polyps
3. Do you have three or more relatives with a history of colon or rectal cancer?
(This includes parents, brothers, sisters, children, grandparents, aunts, uncles, and cousins)

^a Lynch syndrome-related cancers include colorectal, endometrial, gastric, ovarian, pancreas, ureter and renal pelvis, biliary tract, brain (usually glioblastoma), small intestinal cancers, as well as sebaceous gland adenomas and keratoacanthomas.

^b Presence of tumour-infiltrating lymphocytes, Crohn-like lymphocytic reaction, mucinous / signet-ring differentiation, or medullary growth pattern.

Printed with permission: Syngal S, et al. Am J Gastroenterol 2015: 110: 223-262

➤ Performance characteristics for Lynch syndrome utilizing different strategies

Criteria	Sensitivity (range)	Specificity (range)
○ Amsterdam II criteria	0.22 (0.13 - 0.67)	0.98 (0.97 - 1.0)
○ Revised Bethesda Guidelines	0.82 (0.78 - 0.91)	0.77 (0.75 - 0.79)
○ MMR predicted	0.69 (0.68 - 0.75)	0.90 (0.86 - 0.94)
○ MMRPro	0.89 (0.60 - 1.0)	0.85 (0.60 - 1.0)
○ PREMM	0.90 (0.60 - 1.0)	0.67 (0.60 - 1.0)
○ MSI	0.85 (0.75 - 0.93)	0.90 (0.87 - 0.93)
○ IHC	0.83 (0.75 - 0.89)	0.89 (0.68 - 0.95)

Abbreviations: IHC, immunohistochemistry; MMR, mismatch repair; MMRPro, statistical model software that estimates the probability an individual carries such a mutation; MSI, microsatellite instability

Printed with permission: Giardiello FM, et al. Am J Gastroenterol 2014: 109: 1159-1179.



SERRATED POLYPS IN COLORECTUM: BSG Statement

Abbreviation: BSG, British Society of Gastroenterology

East JE, et al. Gut 2017; 0: 1-16.

- Demography
 - Serrated lesions
 - 11 - 53% of all colonoscopy detected polyps
 - Cause 15 - 30% of colorectal cancers (CRCs)
- Types of serrated lesions (SLs)
 - Hyperplastic polyps (HP)
 - Sessile serrated lesion (SSL)
 - SSL plus dysplasia
 - Traditional serrated adenoma
 - Mixed polyps

Note: "Serrated lesions" include HPs and SSL (SSA / Ps).

- Endoscopy

○ Site ○ Small (< 5 mm) pale ○ Sessile / flat ○ Hazy borders	○ Mucus caps ○ Rim of bubbles / debris ○ Pit pattern Kudo pit type II-O

SO YOU WANT TO BE A GASTROENTEROLOGIST!

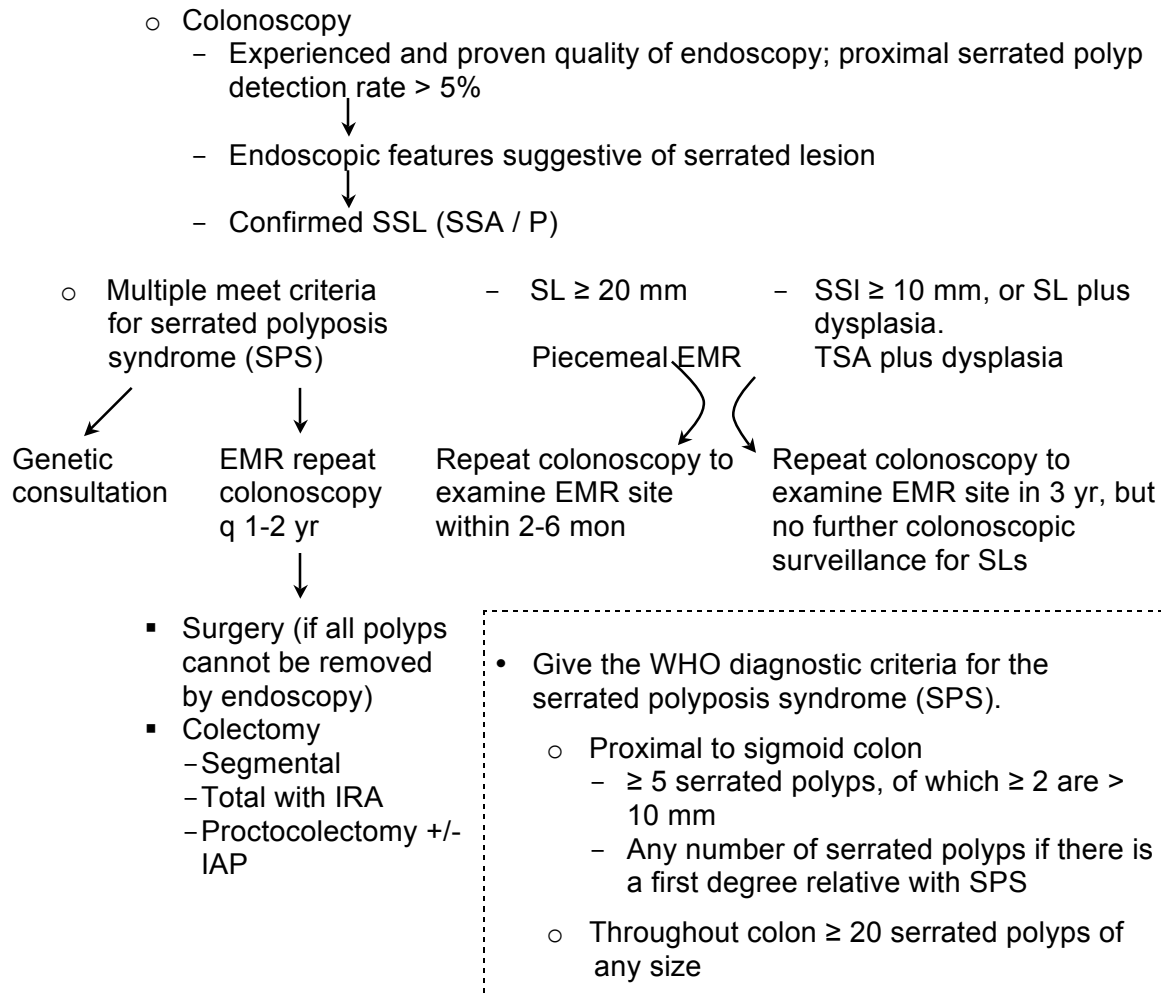
- Give the performance characteristics of identifying to open Kudo pit pattern, type II-O, for diagnosing SSLs
 - Sensitivity ~90% (84 - 97%)
 - Specificity ~75% (66 - 86%)
- Give the endoscopic methods which have been proven to ↑ detection
 - Time to withdraw colonoscope > 6 min
 - Chromendoscopy (indigocarmine dye)
- Histopathology (please see <http://jcp.bmj.com/content/68/8/585.full.pdf+html>)
 - One crypt (AGA), or ≥ 3 crypts, or ≥ 2 adjacent crypts (WHO criteria) which show these histopathological changes in the colonic crypts ("B²D²H²m")

- Branches in crypts - Bases of crypts serrated - Dilation of bases of crypts - Distribution of crypts is irregular	- Herniation through muscularis mucosa - Horizontal extension of bases of crypts (shape of the letter "L" or "T" inverted) - Maturation abnormal



- Within crypts
 - Nuclei
 - Large
 - Crowded
 - Pseudostratified
 - Mitotic activity
- Deep within crypts
 - Disorganized cells
 - Goblet cells
 - Epithelial non-mucus containing epithelial cells
- Superficial (upper) half of crypts
 - Proliferation index
 - MIB-1 positive on immunohistochemistry (IHC)

Average Risk Screening Age ≥ 50 yr



Abbreviations: IAP, ileoanal pouch; IRA, ileorectal anastomosis; SPS, serrated polyposis syndrome SSL, sessile serrated lesion (aka sessile serrated adenoma / polyps [SSA / P]); WHO, World Health Organization



Serrated Lesions of the Colorectum: Cleveland Guidelines

Rex DK, et al. Am J Gastroenterol 2012; 107: 1315-1329.

➤ Classification

- Hyperplastic polyps (HP)
 - Microvesicular hyperplastic polyp (MVHP)
 - The crypts and surface epithelium show a luminal serrated or saw-toothed contour more prominent in the upper levels of the crypts than at the base.
 - The epithelial layer is composed of cells with goblet cell differentiation and others with microvesicular cytoplasmic mucin.
 - Often CIMR high, with BRAF mutations
 - Goblet cell HP (GCHP)
 - After have KRAS mutations
 - Mucin
 - Poor HP
- Serrated
 - Sessile serrated adenoma / polyps +/- dysplasia
 - Proximal colon
 - Premalignant CpG island methylator phenotype (CIMP)
 - Traditional serrated adenoma (TSA)
 - Unclassified
 - Conventional adenoma (tubular, tubulovillous, villous) with a serrated growth pattern

	Number	Size	Colonoscopy
○ Hyperplastic Polyp (HP)			
- Rectosigmoid	≥ 1	< 10 mm	} q 10 yr
- Proximal to sigmoid	≤ 3	≤ 5 mm	
	≥ 4	Any	} q 5 yr
	≥ 1	> 5 mm	
○ Traditional serrated adenoma (TSA)	} < 3 ≥ 1 ≥ 3 ≥ 2	< 10 mm	} q 5 yr
○ Sessile serrated		≥ 10 mm	
○ Adenoma / polyp (SSA / P)		< 10 mm	} q 3 yr
- All locations		≥ 10 mm	



➤ Colonoscopy

- Give the colonoscopic features of hyperplastic, sessile serrated adenoma (SCA) and traditional serrated adenoma (TSA).

Appearance of polyp(s)	Sessile	Flat	Pedunculated	≤ 5 mm	≥ 10 mm	LC	RC	Pre-CRC
○ HP	+	+	-	+	-	+	-	-
○ SSA / P	+	=	-	-	+		+	+
○ TSA	+	-	+	-	+	+	-	+
- Pedunculated			▪ TSA					
- Large			▪ TSA, SSA / P					
- Left colon			▪ TSA, HP					
- Pre-CRC			▪ TSA, SSA / P					

Abbreviations: CRC, colorectal cancer; HP, hyperplastic polyp; RC, right colon; SSA / P, sessile serrated adenoma / polyp; TSA, traditional serrated adenoma

➤ Histopathology

SSA / P	SSA / P with Conventional Adenoma-like Dysplasia	TSA
○ Colonoscopy - Mucus cap - Crypt(s) ▪ Horizontally branched ▪ Distorted, dilated ▪ Inverted maturation ↓ ○ Resection of polyp(s) - Rectosigmoid (RS) > 5 mm - Proximal to RS all suspected SSA / P polyps ↓ ○ Serrated polyposis syndrome (SPS) - WHO recommends ▪ 1st degree relative of SPS patient ▪ Screen - Age 40, or - 10 yr before SPS diagnosed in family member ↓ ○ Post-polypectomy surveillance	○ Ki67-positive ○ May be MLH1-positive, with dysplasia and microsatellite instability ○ Hyperserrated luminal epithelial growth pattern - More pronounced than in microvesicular hyperplastic polyps - The crypts show luminal dilation towards the bases of the crypts, some crypts show horizontal growth along the long axis of the muscularis mucosa (arrow). ○ Goblet cells are present at all levels of the crypts, some of which are dystrophic. Mitotic figures are easily recognized, and located predominantly in the basal aspects of the crypts.	○ Villi – “filiform” (long, bulbous tip) ○ Crypts-budding perpendicular filiform / villous structure (ectopic crypt formation) ○ ↑ eosinophilic cytoplasm ○ Nucleus - Elongated - Basal - Even pattern of chromatin - Epithelium pseudo-stratified ○ May concurrently show dysplasia which is - Adenoma-like, and - Serrated



➤ Treatment

- Endoscopy – Colonoscopy q 1 yr
- Surgery – Extended right hem colectomy, or
– Subtotal colectomy
- Surveillance – Interval personalized based upon risk
- Surveillance of family members – Start
 - ≥ 40 yr, or
 - 10 yr younger than age at diagnosis of the youngest affected relative
 - Interval
 - No polyps at surgery q 5 yr
 - Polyps found at screening
 - Interval more frequent, and personalized based upon risk

Serrated / Hyperplastic Polyposis Syndrome (SPS)

➤ Definition of SPS polyposis

- Proximal to sigmoid colon ≥ 5 SP, ≥ 2 > 10 mm
≥ 1 SP in first degree relative with SPS
- Any site in colon / rectum > 20 SP, any size

SSA / P	}	≥ 2 yr	} q 1-3 yr
SSA / P plus cytological dysplasia		≥ 1 yr	
		≥ 10 mm	
		≥ 1 mm	

Adapted from: Rex DK, et al. Am J Gastroenterol 2012; 107: 1315-29.

➤ Risks (serrated lesions)

- Proximal – Smoking cigarettes
- Distal – Smoking cigarettes
– Low intake of folate
– Low physical activity pathological association

➤ Causes / associations

- Serrated polyps (SP) plus
 - Adenomas
 - HPs
 - Other SCA / Ps
- Proximal SSA / P – Synchronous CRCs with MSI, especially CRCs in proximal colon



➤ Endoscopy

- Sessile or flat
- Size overall < 1 cm
- Left colon > 1 cm

Round Reminders

- It takes an average of 15 yr for SSA/P with no cytological dysplasia to progress to CRC
- SP associated with MSI-high CRC
- Synchronous CRC's more common with SSA/P with cytological dysplasia or CIMP-high CRC

➤ Approach

- Known serrated polyposis
 - ↓
 - Colonoscopy q 1-3 yr
 - Removal of all polyps > 5 mm
 - ↓
 - Colectomy and ileorectal anastomosis
 - Failure of surveillance colonoscopy
 - To control growth of serrated polyps, or
 - Development of CRC

Clinical Considerations

- When HP > 1 cm, consider that it may have been misdiagnosed and is proximal
- Actually a SSA/P, and surveillance colonoscopy should be performed q 3 yr, not q 10 yr
- Patients with both significant polyp findings and concurrent adenomas may be advanced stage in the progression toward cancer Closer follow-up may be indicated in some cases based on clinical judgement.

Rex DK, et al. Am J Gastroenterol 2012; 107: 1315-1329, footnote to Table 5.



HARMARTOMATOUS POLYPS

Peutz-Jeghers Syndrome (PJS)

- At risk or affected PJS patient (STK 11 mutations)



“Regular” surveillance

- GI
 - Stomach
 - Small bowel
 - Colon
- F-GU
 - Breast
 - Ovary
 - Pancreas
 - Use AGA guidelines for surveillance of hereditary pancreatic cancer
 - Uterus
 - Cervix
- Lung (no evidence-based recommendation, but
 - Annual chest x-ray or CT chest suggested in smokers)

Abbreviation: F-GU, female genitourinary system and breast

Cowden Syndrome (CS, aka PTEN Hamartoma Tumour Syndrome)

- Give the indications for genetic evaluation for Cowden (PTEN hamartoma tumour) syndrome.
 - Skin (Mucocutaneous)
 - Trichilemmoma (1 proven biopsy) or
 - Palmoplantar keratosis, multiple or
 - Papillomatosis
 - Multiple or oral mucosa
 - Papules, multiple, facial
 - Macular pigmentation of glans penis
 - Breast cancer
 - Thyroid follicular cancer
 - GI multiple hamartomas
 - GU endometrial cancer
 - Family with PTEN mutation
 - Syndromes
 - Bannaayan-Riley-Ruvalcaba (BRRS)
 - Adult Lhermitte-Duclos disease (ALD)
 - Autism spectrum disorders plus macrocephaly (ASDM)
 - Macrocephaly plus ≥ 1 major criteria
 - 1 major plus ≥ 3 minor
 - ≥ 3 major plus ≥ 4 minor

Juvenile Polyposis Syndrome (JPS)

- Number of juvenile polyps
 - ≥ 5 in colorectum
 - ≥ 1 in any other part of GI tract



- Test for mutations
 - SMAD4
 - BMPR 1A



LARGE NON-PEDUNCULATED COLORECTAL POLYPS (LNPCPS): ACPGB / BSG / NICE GUIDELINES

Abbreviations: ACPGB, Association of Coloproctologists of Great Britain; BSG, British Society of Gastroenterology; NICE, National Institute of Health and Care Excellence

Rutter MD, et al. Gut 2015; 64(12):1847-73.

➤ Terminology

- Non-pedunculated colorectal polyp (NPCP)
 - Better term than “flat” or “sessile”
- Large non-pedunculated colorectal polyp (LNPCP)
 - Pit pattern (Kudo) or NICE NBI classification
- Additional description
 - Paris classification (polyp morphology)
 - Laterally spreading type polyp (LST)
 - Pit pattern (Kudo) or NICE NBI classification

➤ Risk stratification

- ↑ risk of malignancy
 - Paris classification o-IIc / o-IIa + IIc morphology
 - LST
 - LST-G (granular)
 - LST-NG (non-granular)
 - Pit pattern II
 - Surface
 - Distorted
 - Colour / vessels (NICE NBI type III)
 - Microvessels thick / irregular (Sano capillary pattern III)
- Complex NPCP
 - ↑ risk
 - Malignancy, incomplete resection / recurrence, adverse event
 - SMSA level 4 (size, morphology, access)
- ↑ risk of incomplete resection / recurrence
 - Size
 - > 4 cm
- Guideline-based adherence to quality measures
- Multidisciplinary meetings
- Regular audit to ensure key performance indicators
- Measure and photograph lesion
- Digital, chromoendoscopy (methylene blue, indigo carmine)



- First-line therapy of LNPCPs
 - If malignancy not suspected
 - Endoscopic resection
 - If malignancy expected
 - Avoid piecemeal resection
- Careful acquisition of mucosal biopsies, avoid
 - Flat lesions or edges of lesions
 - Tunnel biopsies (biopsy on biopsy)
- Insufflation
 - CO₂
- Submucosal lifting solution
 - Colloidal, with adrenalin
- Anti-coagulation guideline-based
 - Stop
 - Antiplatelet drugs for 7 days
 - Anti-coagulants for 5 days (INR < 1.5)
 - Do not stop ASA if indication is sound
 - LMWH for high-risk persons, as per guidelines
- Consider introducing scoring system assess polyp difficulty

Please see to details of the L-NPCP resection in the paper quoted

- Consider monitoring key performance indicators (KPI)

KPI	Suggested Minimum Standard
○ Recurrence / residual polyp at 12 mon of LNPCP removed endoscopically	< 10%
○ Complications (EMR)	
– Perforation	< 2%
– Bleeding post-procedure	< 5%
○ Time lines for referral	
– Diagnosis to referral for advanced endoscopy	< 4 wk
– Diagnosis to completion of advanced endoscopy	< 8 wk



ACUTE UNCOMPLICATED DIVERTICULITIS (AUD): AGAI GUIDELINES

Abbreviations: AGAI, American Gastrointestinal Association Institute

Stollman N, et al. Gastroenterology 2015; 149: 1944-49; and Strate LL, et al. Gastroenterology 2015; 149: 1950-76.

➤ Definition

- Clinically evident macroscopic inflammation of a diverticulum or diverticula

➤ Demography

- Occurs in ~4% of patients with diverticulosis
 - 15% of these have complicated disease (abscess, perforation, fistula, or colonic obstruction)
 - 15-30% have recurrence
- Presumptive clinical diagnosis of AUD
Selective ≥ 7 day course of broad-spectrum IV antibiotics (2/3 generation cephalosporin plus metronidazole or carbapenem, or piperacillin / tazobabactam)
 - ↓
 - po cefadroxyl
 - ↓
 - 4-8 wk post-resolution of AUD: colonoscopy to exclude CRC
 - ↓ risk of recurrent event
 - ↓ 20% in 5 yr
 - If recurrence, repeat medical therapy

	Third attack (second recurrence)
○ Elective respective-short term	10%
○ Surgical patient-by-patient-long-term	20%
○ Risk of fourth attack	< 5%
 - Uncertain evidence for
 - Diet
 - High-fibre diet
 - Avoiding corn, nuts, popcorn
 - Probiotics
 - Rx
 - Aspirin, NSAIDs, mesalamine, rifaximin
 - Exercise

Abbreviations: AUD, acute uncomplicated diverticulitis; CRC, colorectal cancer; Rx, medication; SIRS, systemic inflammatory response syndrome

➤ Summary

- The strength of these recommendations is conditional, except for that related to not using mesalamine after AUD. The quality of evidence is moderate for mesalamine, but for all others the quality is low or very low.
- Colonoscopy should be performed after resolution of acute diverticulitis in appropriate candidates to exclude misdiagnosis of colonic neoplasm if a high-quality examination of the colon has not been recently performed.



- Uncomplicated disease confirmed by CT
 - Excluded outpatients and patients with complicated disease
 - Abscess of fistula
 - Severe infection / sepsis
 - Immunosuppression
 - Significant comorbidities
- Tumour in patients with recent acute diverticulitis
 - Advanced adenomas 38/10³
 - Colorectal cancer 15/10³
- Absence of mass on CT doesn't exclude possibility of underlying colonic neoplasm
- Alternative non-neoplastic explanations (IBD or ischemic colitis) infrequently identified
- No reported data on recurrent diverticulitis or colonic perforation rates in this setting
- Factors that may influence decision to perform a colonoscopy
 - Timing and completeness of prior colonoscopy
 - Comorbidities
 - Persistent symptoms of abdominal pain or diarrhea
 - Patient preference
- Risk of colonoscopy may be higher in chronic diverticulitis, acute recurrent diverticulitis, or complicated diverticulitis
- Surgical resection after an attack of AUD
 - ~20% of patients have recurrent episode of diverticulitis within 5 yr
 - Low risk (~5%) of future diverticular complications and need for emergency surgery if treated medically without colonic resection
 - ~10% of patients with elective sigmoid resection have short term post-op complications
 - Wound infection, anastomotic leak, cardiovascular disease, and fecal incontinence
 - Increase risk in patients > 65 yr of age
 - ~25% have long-term complications:
 - Abdominal distention, cramping, altered defecation, and fecal incontinence
 - Magnitude of benefit of reduction of risk of recurrent diverticulitis after elective surgery unknown
- Do's and don't's
 - Do exercise vigorously
 - Don't use
 - Non-ASA NSAIDs
 - Data from limited observational studies = moderately increased risk of occurrence of an episode of any episode of diverticulitis and complicated diverticulitis with non-ASA NSAIDs



- Aspirin
 - Observational studies indicate slightly increased risk of occurrence of any episode of diverticulitis (RR 1.25; 95% CI 1.05-1.47); however the estimate of risk of complicated diverticulitis is less certain (RR 1.13; 95% CI 0.61-2.10)
 - Modest protective effects of ASA on overall mortality and non-fatal MI tempered by modest increase in GIB → value of ASA as secondary prevention in CAD well established and in this setting would outweigh any increased risk of recurrent diverticular disease
 - Value of ASA as primary preventive measure less certain and would require more individualized decision-making
- Mesalamine
 - Mesalamine (anti-inflammatory agent) studied due to inflammatory changes present histologically in acute diverticulitis
 - 6 studies have evaluated > 1800 patients
 - Current available evidence moderate in quality and more robust than most of the other agents evaluated in this guideline, does not suggest efficacy in reducing the risk of recurrence, resolution of pain, or need for surgery in this specific population
 - Role of mesalamine in patients with multiple recurrent / relapsing diseases or patients with symptomatic uncomplicated diverticular disease has not been addressed in this guideline, and this recommendation does not apply to those populations
- Probiotics
 - One small trial evaluating use of probiotics in patients with a history of diverticulitis reported a numeric, but not statistically significant, reduction in recurrence, and another unblinded trial had similar findings
- Rifamixin
 - Rifaximin (non-absorbable oral antibiotic) studied in this population in 1 unblinded study that was terminated early
 - Trial reported numeric reduction in recurrence rates but results not statistically significant and effect still uncertain (in addition to its costs and potential adverse events)
 - Thus this guideline suggest against its routine use in this population to reduce recurrence rates, pending further study
 - Similar to (potential) role of mesalamine, efficacy of rifaximin in patients with chronic recurrent symptoms of symptomatic uncomplicated diverticular disease has not been addressed in this guideline, and this recommendation does not apply to those populations
- Physical activity
 - Large observational study of 47,288 men indicated modest decreased risk of occurrence of any episode of diverticulitis among those with vigorous activity levels
- Special diets (high fibre, low nuts or popcorn)
 - Single, small case-control study showed benefit of fibre for chronic abdominal pain in patients with diverticulosis inconsistent, but intake of high-fibre diet or fibre supplementation unlikely to pose substantial risk to patients
 - Key study reported modest estimates of relative risks of nuts and popcorn consumption (range 0.55-1.13) and high degree of statistical uncertainty (95% CI surrounding 1.0)



COLONIC ISCHEMIA (CI): ACG GUIDELINES

Abbreviations: ACG, American College of Gastroenterology

Brandt LJ, et al. Am J Gastroenterol 2015; 110: 18-44.

- Suspicion of CI
 - Sudden abdominal pain (87%), usually before bleeding (84%), diarrhea (56%), nausea (30%)
 - Common presentations
 - RCI – Abdominal pain without rectal bleeding
 - Non RCI – Hematochezia
 - Hematochezia: suspect non-isolated right colon ischemia
 - Especially in high-risk groups with comorbidities
 - CV disease
 - Diabetes
 - IBS
 - Thrombophilia (young persons)
 - Surgery on IMA (AAA, abdominal surgery)
 - Anti-constipation drugs
 - Rx
 - Immunomodulators
 - Street (illicit)
 - Drugs
 - Long-distance
 - Sickle cell crisis

MCQ Trick

Chronic obstructive pulmonary disease (COPD) and chronic renal failure (CRF) are associated with ↑ mortality if they develop CI, but COPD/CRF do not ↑ risk of CI



- Laboratory testing suggesting ↑ severity of CI
- Diagnostic imaging
 - CT with contrast showing thick colonic wall, edema, thumb printing; distribution (stop endoscopy at distal-most extent of disease)
 - CTA colonic pneumatosis, portomesenteric gas
 - Conventional splanchnic angiography
 - Warning signs of imminent AMI: severe pain (IRC) plus AF



- Colonoscopy with 48 h, using minimal air insufflation, and take biopsies, unless evidence of
 - Gangrene
 - Pneumatosis

Abbreviations: AAA, abdominal aortic aneurysm; AF, atrial fibrillation; AMI, acute mesenteric ischemia; CTA, multiphasic CT angiography; CV, cardiovascular; IBS, irritable bowel syndrome; IMA, inferior mesenteric artery



➤ Supportive care, combination antibiotics



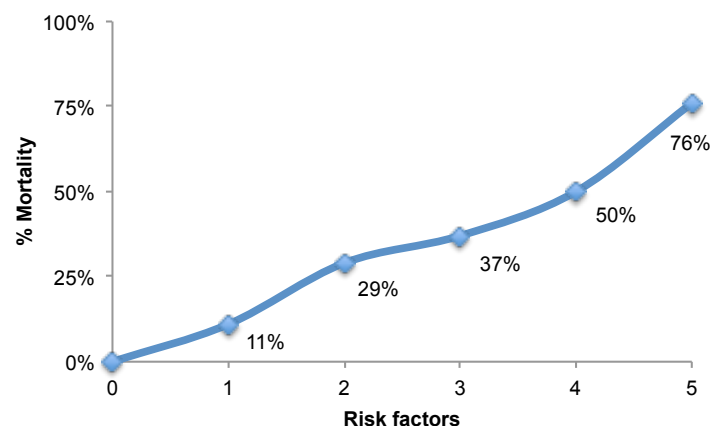
- Consider early surgical management (narcotic bowel) if:



- Clinical sign
 - Hypotension (SBP < 90 mmHg)
 - Tachycardia (HR > 100 bpm)
 - Pain with no bleeding (IRCI)
 - Peritoneal signs
 - Massive bleeding
- Diagnostic imaging
 - IRCI
 - Pancolonic CI
 - Presence of gangrene portal venous gas pneumatosis intestinals
 - Fulminant colitis +/- toxic megacolon
- Laboratory
 - BUN > 20 mg/dL
 - HfB < 12 g/dL
 - WBC > 15×10^9 cells/mm³
 - LDH > 3500 U/L
 - Na⁺_s < 136 mEq/L
- Colonoscopy
 - Colonic mucosa ulcerated

- Estimate risk of surgery for acute indications using Ischemic Colitis Mortality Risk (ICMR) factors:

- Overall surgical risk ~ 50%
- Cardiac EF < 20% (ECHO)
- Acute kidney injury (AKI)
- Lactate (preoperative) > 2.5 mmol/L
- Rx pre- / intraoperative catecholamines given
- Subtotal / total colectomy



❖ Acute

❖ Chronic indications

- Symptoms from colonic strictures

For stricture transendoscopic dilation, or repeat surgery for symptomatic stricture

❖ Subacute indications

- Symptoms 2-3 wk after resection for acute segmental colitis
- Protein-losing colopathy

Surgical Resection

Commonest Procedure	In-hospital Mortality
- Total / subtotal colectomy	12%
- R. hemicolectomy	38%
- Segmental colectomy	35%

or

- Primary anastomosis
- Diverting stoma

Abbreviations: ASA, American Society of Anesthesiologists; bpm, beats per minutes; BUN, blood urea nitrogen; Hgb, hemoglobin; HR, heart rate; IRCI, isolated right-colon ischemia LDH, lactic dehydrogenase; Na⁺_s, serum sodium concentration; SBP, systolic blood pressure



DISORDERS OF GUT-BRAIN INTERACTION (DGBI)

Schmulson MJ and Drossman DJ. J Neurogastroenterol Motil 2017; 23: 151-63.

➤ Definitions

- Symptom
 - “... an experience perceived as different from normal”
- Syndrome
 - “... a consistent association of symptoms”
 - Based on Rome IX on population cluster analysis and clinical trials
- Note
 - Irritable bowel syndrome diarrhea predominant (IBS-D) and irritable bowel syndrome constipation predominant (IBS-C) are part of a spectrum

➤ Demography

- Using Rome IV criteria, prevalence of IBS in Canada is ~6% of adult population

➤ Types of IBS

IBS subtypes	Bristol Stool Type	
	> 25%	< 25%
○ IBS-C	1 – 2	6 – 7
○ IBS-D	6 – 7	1 – 2
○ IBS-M (mixed)	1 – 2	6 – 7
○ IBS-U (unclassified)	– Bowel habits cannot be accurately categorized	

➤ Diagnostic criteria

- “Recurrent abdominal pain on average at least 1 day / week in the last 3 months”, associated with ≥ 2 of the following
 - Related to defecation
 - Associated with a change in
 - Frequency and form of stool



CENTRALLY MEDIATED DISORDERS OF GASTROINTESTINAL PAIN (CAPS)

Dinosaur term “ Functional Abdominal Pain Syndrome”

- Definition
 - Symptom associated probability (SAP)
- Types
 - Functional dyspepsia (EGD -ive)
 - Functional heartburn
 - pH- / SAP-
 - Reflux hypersensitivity
 - pH- / SAP+
 - Unexplained lower-abdominal pain with no change in bowel frequency or form
- Pathophysiology
 - Central sensitization leading to ↓ inhibition (disinhibition) of pain signals
- Clinical
 - Describe the characteristics of the patient and their pain in CAPS
 - Pain
 - Urgent
 - Intense
 - (Described with verbal as well as non-verbal methods)
 - Patient
 - Seeking
 - Healthcare
 - Narcotic
 - Test
 - Cure
 - Takes minimal responsibility for self-management
 - Psychiatric comorbidity
- Treatment
 - Maintain good patient-physician relationship
 - Non-pharmacological
 - Cognitive behaviour therapy
 - Hypnosis
 - Mindfulness therapy
 - Psychodynamic interpersonal psychotherapy
 - Pharmacological
 - Tricyclic antidepressants (TCAs)
 - Serotonin norepinephrine reuptake inhibitors (SNRIs)



IRRITABLE BOWEL SYNDROME (IBS)

Abbreviation: ACG, American College of Gastroenterology

Ford AC, et al. Am J Gastroenterology 2014; 109 Suppl 1:S2-26.

➤ Definition (Rome IV)

- Recurrent abdominal pain / discomfort ≥ 3 d/mon in the past 3 mon with symptom onset ≥ 6 mon before diagnosis, plus ≥ 2 of the following
 - Onset associated with altered frequency / form of stool
 - $\downarrow$ pain / discomfort with defecation

➤ Evidence-based treatment

○ Diet

Test Diet	Test vs Placebo	Therapeutic Gain
- Low FODMAP diet	68% vs 23%	45%
- Gluten-free diet	68% vs 40%	28%
- Psyllium fibre	57% vs 35%	22%
- Exclusion diet	28% vs 17%	11%
- Probiotics improve bloating, flatulence, global symptoms		

NNT

○ Indications	9
- Rifaximin	~5
- Antispasmodics	~3
- Peppermint oil	
- Antidepressants	
▪ TCAs	4
▪ SSRIs	4
- Serotonergic agents (5-HT ₃ antagonist)	
▪ Alosetron	3
▪ Cilansetron	6
▪ Ramostetron	7
- IBS-C	
▪ Liniclotide	6
▪ Lubiprostone	12.5
○ Psychological therapy	
- Cognitive behaviour therapy	3
- Dynamic psychotherapy	3.5
- Hypnotherapy	4
- Multi-component psychological therapy	5
- IBS-D (females)	

Abbreviations: d, day; FODMAP, fermentable oligosaccharides, disaccharides, monosaccharides, and polyols; mon, month; NNT, number needed to treat; SSRI, selective serotonin reuptake inhibitors; TCA, tricyclic antidepressants;



Therapy		IBS (OR, 95% CI)	CIC
○ Diet			
– Psyllium fibre		0.86 (0.80 - 0.94)	0.25 (0.16 - 0.37)
– Gluten-free / FODMAP exclusion diet (IgG based)		0.83 (0.73 - 0.94)	
– Probiotics		0.79 (0.70 - 0.89) [2]	
– Peppermint oil		0.51 (0.33 - 0.70) [4]	
○ Psychological intervention ¹		0.65 (0.61 - 0.76)	
– Biofeedback			0.33 (0.22 - 0.50)
○ Antispasmodics		0.69 (0.59 - 0.81) [5]	
○ Antidiarrheals (TCA, SSRI)		0.67 (0.58 - 0.77) [NNT 3-4]	
– Loperamide			
– Laxative [3]			
– 5-HT ₃ (withdrawal) antagonists [3]			
– 5-HT ₄ agonist [6]			
○ Promotility			
– Prucalopride			0.81 (0.75 - 0.86)
○ Prosecretory			
– Linaclotide ²		0.80 (0.75 - 0.85) [6]	0.89 (0.80 - 0.87)
– Lubiprostone ³		0.91 (0.87 - 0.95) [4]	0.67 (0.58 - 0.77)
– PEG		-	0.52 (0.41 - 0.65)
– Lactulose		-	0.48 (0.27 - 0.86)
○ Antibiotics			
– Rifaximin		0.84 (0.78 - 0.90) [9]	
– Neomycin		0.73 (0.56 - 0.96) [5]	
○ Psychological therapy	NNT	OR (IBS)	
- Cognitive behaviour therapy	3	0.050 - 0.7	Peppermint
- Hypnotherapy	4	(medium	Antispasmodics /
- Multi-component psychological therapy	4	efficacy)	Antidiarrheal
			Psychological
			intervention
- Dynamic psychotherapy	3.5	0.7 - 0.86 (low efficacy)	Prosecretory /
			Antibiotics
			Diet
○ Linaclotide	– A 14 amino acid peptide which is structurally similar to the guanylin family of peptides – ↑ activity of guanylate-cyclase-C-receptors on BBM → ↑ GMP_c → ↑ CFTR activity → ↑ secretion of Cl⁻ / HCO₃⁻ → ↑ secretion of water from crypts of small bowel		
○ Lubiprosterone	– Activates CIC2 (chloride channel type 2 on BBM of enterocytes)		

Abbreviations: 5-HT₃, serotonin subtype 3; BBM, brush border membrane of enterocytes; CFTR, cystic fibrosis transmembrane conductance regulator; CI, confidence interval; Cl⁻, chloride; FODMAP, fermentable oligosaccharides, disaccharides, monosaccharides and polyols; GMP_c, cyclic guanosine monophosphate; HCO₃⁻, bicarbonate; IBS-C, irritable bowel syndrome-constipation predominant; ISE, insufficient evidence; NNT, number needed to treat; PEG, polyethylene glycol; RR, relative risk; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressants



CHRONIC IDIOPATHIC CONSTIPATION (CIC): ACG Monograph

Abbreviations: ACG, American College of Gastroenterology

Ford AC, et al. Am J Gastroenterology 2014; 109 Suppl 1:S2-26.

➤ Definition

- Rome IV defines functional constipation as: the presence of two or more of the following:
 - Straining during at least 25 % of defecations
 - Lumpy or hard stools in at least 25 % of defecations
 - Sensation of incomplete evacuation for at least 25 % of defecations
 - Sensation of anorectal obstruction / blockage for at least 25 % of defecations
 - Manual maneuvers to facilitate at least 25 % of defecations (e.g., digital evacuation, support of the pelvic floor)
 - Fewer than three defecations per week

These criteria should be fulfilled for the past 3 months with symptom onset at least 6 months before diagnosis

	NNT
○ Medications	
– Soluble fibre, psyllium	2
– Sodium pico sulfates, bisacodyl	3
– Polyethylene glycol	3 / 4
– Lubiprostone	4
– 5-HT4 agonist	6
– Linaclotide	6
○ Biofeedback for pelvic floor dysynergia-proven effective	

“Our greatest glory is not in never failing,
but in rising up everyt time we fall.”

Ralph Waldo Emerson



Anorectal Disorders: ASGE Guidelines

Abbreviation: ASGE, American Society for Gastrointestinal Endoscopy

Appalaneni V, et al. Gastrointestinal Endoscopy 2010; 72: 1117-1123.

❖ Anal Fissure (Chronic)

- Apply nitrate or calcium channel blocker to affected area, or
 - Injection of botulinum toxin

↓ poor response

- Lateral internal sphincterotomy

❖ Fecal incontinence

- DRE, colonoscopy or flexible sigmoidoscopy

↓

- Evaluate sphincter integrity EUS or MRI

❖ Internal hemorrhoids with bleeding

↓

Rubber band ligation (RBL), or sclerotherapy

❖ Radiation proctopathy

- Symptoms / signs which affect patient's quality of life

↓

- Endoscopic argon plasma coagulation (APC)

↓

- Topical formalin

↓

- Hyperbaric oxygen therapy

Abbreviations: APC, argon plasma coagulation; DRE, digital rectal examination; MRI, magnetic resonance imaging; RBL, rubber band ligation



LOWER GI BLEEDING: ASGE GUIDELINES

Abbreviation: ASGE, American Society for Gastrointestinal Endoscopy

Pasha S, et al. Gastrointestinal Endoscopy 2014; 79: 875-85.

- Suspected lower GI bleeding
 - EGD, plus
 - Colonoscopy within 24 hr of presentation after rapid bowel preparation
 - Sigmoidoscopy may be adequate in patients if:
 - > 50 yr
 - No alarm symptoms
 - Normal DRE and
 - Chronic intermittent scant hematochezia
- ↓
- Endoscopic treatment
 - Options
 - Epinephrine / saline injection plus
 - Either thermal coagulation or placement of endoscopic clip
 - Argon plasma coagulation (APC) for bleeding angioectasias
 - For bleeding diverticulum (or resected polyp site)
 - Mark bleeding site with tattoo or clip
- ↓
- If no bleeding site found or site found but severe bleeding that cannot be controlled endoscopically
- Therapeutic angiography, or surgical intervention

“The teacher who is indeed wise does not bid you to enter
the house of his wisdom but rather leads you
to the threshold of your mind.”

Khalil Gibran



Colonoscopy for Lower GI Bleeding

➤ Demography

- Incidence, overall 35 / 10⁵
- Mortality rate < 2%

❖ Diverticular Bleeding

- Usually L-side
- May be precipitated by NSAIDs
- Occurs spontaneously ~ 80%
- Rebleeding within 4 yr ~ 40%
 - Late rebleeding after endoscopic clipping ~ 20%

Note:

- Before diagnosing a diverticular bleed look for:
 - Signs of active bleeding from a diverticulum, or
 - High risk stigmata

MCQ Alert

- In the patient with hematochezia ~ 15% are due to a lesion in the upper GI tract
- Be particularly alert to thinking about an upper GI source of hematochezia if the patient is hypotensive
- For this reason, it is often appropriate to pass a NG tube to attempt to aspirate blood in order to demonstrate an upper GI source which may require endoscopic hemostatic therapy

Another Clinical Tips

- In the patient with hematochezia, if the NG aspirate is stained with bile but no blood, the cause of the lower GI bleeding is not likely to be on upper GI source



- Risk stratification
- Give the clinical features which suggest the patient is high risk for a poor prognosis
 - Physical signs
 - Heart rate ≥ 100 bpm
 - SBP $< 100 - 115$ mm Hg
 - History
 - Rectal bleeding
 - Gross bleeding
 - Bleeding within first 4 hr of evaluation
 - Syncope
 - Aspirin use
 - Multiple comorbidities

Melena and Endoscopy

- Give what's next after negative EGD/colonoscopy in the patient with melena:
 - Melena (black blood in the stool) may be from upper or right-sided lower GI tract diseases
 - If the EGD is negative, perform colonoscopy, particularly to exclude colorectal cancer (CRC)
 - After “bidirectional” endoscopy (EGD/colonoscopy), consider investigating for possible small bowel source of bleeding

❖ Ischemic Colitis

- Mechanisms
 - Hypotension / hypovolemia → vasospasm
 - Obstruction of mesenteric vessels
 - Embolus
 - Thrombus (including hypercoagulable states)
- Sites
 - “watershed” areas
 - Splenic flexure
 - Rectosigmoidal junction



- Endoscopy
 - Usually rectal sparing
 - Sharp out-off between ischemic and non-ischemic colon
 - No diagnostic / pathognomonic finding
 - Suggestive changes
 - Redness / friability
 - Ulceration, especially
 - Linear ulcer
 - Longitudinal anti-mesenteric (“single-strip” sign)
- Diagnostic imaging
 - Give the indications for performance angiography in the context of ischemic colitis:
 - Severe ischemic colitis (IC)
 - R-sided IC
 - Associated small intestinal ischemia
 - Thromboembolism as suspected causative factor
- ❖ **Angioectasia** (aka angiodysplasia, vascular ectasia)
 - Demography
 - Older persons
 - Cause of ~ ½ of severe LGIB (hematochezia)
 - Pathogenesis
 - Intermittent mild obstruction of submucosal blood vessels → dilated vessels
 - R. sided > L. sided
 - Control feeding vessel
 - Endoscopic
 - 80% sensitive, except when ↓ bloodflow (blood loss, sedation) prevents visualization
 - Argon coagulation
 - Non-contrast
 - Small / large vessels
 - Predictable depth levels (ectatic vessels are submucosal)
 - 3645 W, 1 L Argon / min
 - Place probe 1-3 mm from mucosal surface
 - Pulses q 1-2 sec



- Non-endoscopic
 - Severe, unstable, failed endoscopic hemostatic therapy
 - Mesenteric angiography
 - Minimum 0.5 mL/min bleeding
 - Superselective embolization
 - Successful cessation of bleeding
 - Diverticular 83%
 - Non-diverticular 50%
 - Rebleeding ~ 20%
 - Diverticular ~ 20%
 - AVM ~ 40%
 - Multi-detector row CT
 - Superior to nuclear RBC scan
 - Nuclear RBC scan
 - Minimum 1 mL/min bleeding for detection
 - Surgery
 - No diagnosis of cause
 - Failed (hypertension / shock) endoscopic / superselective embolization therapy
 - ≥ 6 units PRBC units transfused
- } Acceptable surgical risk

Abbreviations: AVM, arteriovenous malfunction / angiectasias; PRBC, packed red blood cells; RBC, red blood cells

❖ Hemorrhoids

- Definition
 - “Plexus of dilated arteriovenous inferior and superior internal hemorrhoidal veins in the submucosal of the distal rectum”

❖ Post-polypectomy Bleeding

- Demography
 - ~ 9/1000 colonoscopies with polypectomy



❖ Rectal Ulcers

- In ICU patients who develop rectal bleeding, up to 1/3 have solitary rectal ulcers (which are often multiple in number)
- Associated conditions (comorbidities):
 - Lung ■ Respiratory failure
 - Liver ■ Cirrhosis, decompensated
 - Kidney ■ End stage renal disease (ESRD), on dialysis
 - Malignancy
- Prognosis
 - Rebleeding ~ 45%
 - Death ~ 45% (from acute bleeding or visible vessel)

❖ Radiation Proctopathy

- Give the pathological lesions which lead to radiation proctopathy.
 - Radiation → Endarteritis obliterans
 - Neovascularization
 - Telangiectasias

❖ Crohn Colitis

- Give the prognosis of rectal bleeding occurring from Crohn colitis.
 - Spontaneous cessation (1/2)
 - Rebleeding (1/3)

❖ HIV / AIDs-associated Rectal Bleeding

- Demography
 - HIV / AIDs is an uncommon cause of lower GI bleeding, but the inpatient mortality rate is high (~ 30%)
- Causes / associations

○ Infection - CMV, HSV ○ Infiltration - Kaposi sarcoma ○ Ideopathic - Proctocolitis	}	Usually in association with AIDs-related thrombocytopenia



Quality Colonoscopy

- Suggested bowel preparations
 - Polyethylene glycol (PEG)
 - Electrolyte solutions (ELS)
 - Split or full dose
 - High or low volume (SD 'sports dose', low volume) +/- bisacodyl
 - Others
 - Oral sodium sulfate (OSS)
 - Sodium sulfate plus sulfate-free (SF) PEG-ELS
 - Sulfate free
 - Picosulfate / magnesium oxide / anhydrous citric acid
 - Magnesium citrate
 - Sodium phosphate
- } Not in renal failure

Endoscopy Report of Quality of Bowel Preparation

- Types of bowel preparation scale
 - Aronchick
 - Boston
 - Ottawa

Clinical Gem

- Do not use NSAIDs before colonoscopy
- Do not use phosphate containing preparations for colonoscopy
- May result in mucosal changes suggestive of IBD



GALLBLADDER AND BILIARY TREE



GALLSTONE DISORDERS: EASL / NICE GUIDELINES

Abbreviations: EASL, European Association for the Study of the Liver; NICE, National Institute for Health Care Experience

EASL. J Hepatology 2016; 65: 146-181; NICE: www.nice.org.uk/guidance/cg1888, 2014.

- Types of gallstones
 - Cholesterol
 - Black pigment
 - Hemolytic disorders
 - Hepatic cirrhosis
 - Brown
 - Post-cholecystectomy
 - Sclerosing cholangitis
 - Chronic infectious ("oriental") cholangitis
- } Formed in gallbladder
- } Formed in CHD, CBD
-
- Causes / associations
 - Metabolic syndrome (MS)
 - Independent of MS
 - Diet
 - Hormone replacement therapy (HRT; estrogen-only formulations)
 - "Fast foods"
 - ↓ fibre
 - ↓ poly- / monounsaturated lipids
 - ↓ vitamin C intake
 - ↓ physical activity
 - ↓ HDL concentrations
 - Rapid weight loss
 - Bariatric surgery
 - Extreme dieting

Little-known Fact

Diet supplementation with vitamin C 500 mg qid → ↓ risk of ultrasound-demonstrated gallstones by ~40.



Bariatric Surgery and Gallstone Disease

- ~ ¼ of persons having bariatric surgery (RYGB, VBG, ABG) develop gallstones over 3 yr
 - Usually in first 7-18 mon
 - 20% become symptomatic and require cholecystectomy
- UDCA can prevent gallstone formation in bariatric surgery

Abbreviations: AGB, adjustable gastric banding; BMI, body mass index; DMT2, diabetes mellitus type 2; HDL, high density lipoprotein; RVGB, Roux-en-Y gastric bypass; UDCA, ursodeoxycholic acid; VGB, vertical band gastroplasty

MCQ TIP

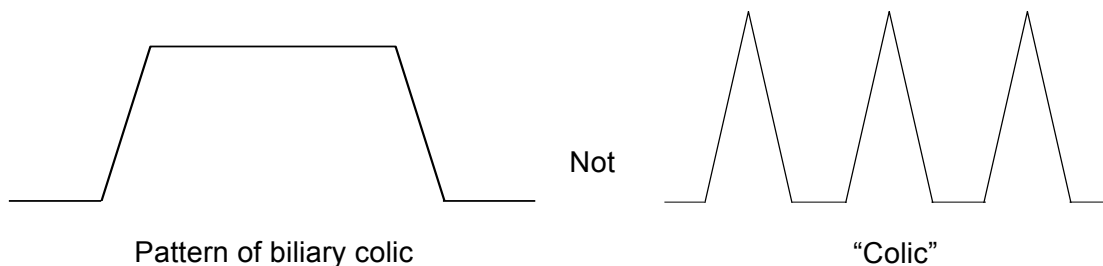
- UDCA may be used to ↓ risk of formation of gallstones
 - Post-bariatric surgery
 - Long-term use of somatostatin
 - ABCB4 genetic changes → low phospholipid-associated cholelithiasis (LPAC)

SO YOU WANT TO BE A GASTROENTROLOGIST!

- Persons with the ABCB4 genetic change procedure lower phospholipid levels in bile, lithogenic bile and ↑ risk of gallstones. Give the clinical characteristics which suggest the ABCB4 and the need for UDCA:
 - Cholesterol gallstones before 40 yr
 - Intrahepatic bile duct stones
 - Recurrent biliary symptoms post-cholecystectomy

Biliary Colic

- Definition
 - Recurrent (50%) episodes of severe pain in RUQ / epigastrium, starting suddenly ~ 1 hr pc, increasing progressively and then stabilizing, lasting > 15 – 30 min, radiating to the right shoulder / back, and improved / relieved with analgesics
- Give why biliary colic is not actually “colic”.



➤ Demography

- Gallstones present in ~ 15% of “Western” countries
- 20% become symptomatic within 20 yr
 - Annual risk 0.7 – 2.5%
 - Annual risk of complications 0.1 – 0.3%

➤ Clinical

- Suspect gallstones for cause of symptoms

	OR	95% CI
– Biliary colic	2.6	2.4 - 2.9
– Radiating pain	2.8	2.2 - 3.7
– Benefit of analgesics	2.0	1.6 - 2.5

- Exception

- Typical pain may not be present with
 - ↑ age
 - Atypical symptoms
 - Immunosuppression

Abbreviations: CI, confidence interval; OR, odds ratio

➤ Diagnosis

- Clinical Suspicion

“Episodic attacks of severe pain in the right upper abdominal quadrant or epigastrium for at least 15 - 30 min with radiation to the right back or shoulder and a positive reaction to analgesics”

- Abdominal ultrasound
- Liver biochemistry, as indicated



- NSAIDs
- Plasmolytics
- No need for prophylactic antibiotics



- Early (within 72 hr) elective, laparoscopic, cholecystectomy, or
 - Mini laparotomy (< 8 cm) cholecystectomy
 - Drug surgery
 - 2 ports ≥ 10 mm, plus
 - 2 ports ≥ 5 mm
 - Preferred approach in Child-Pugh A / B cirrhotic
- Surgical bile duct exploration
 - Not indicated for low risk CBD stones
 - High risk stones
 - Surgical exploration
 - Primary closure of CBD (rather than T-tube drainage)
 - Accidental spillage of stones into abdomen – remove
 - No need to convert to open cholecystectomy



Special Considerations

- Pregnancy Lap' Chole' at T1, 2 or T3 if indication is urgent
- Elderly, high anesthetic risk, with high risk acute cholecystitis, gallstone pancreatitis, CBD obstruction

Clinical Gems

- Biliary colic may be associated with symptoms other than the typical pain pattern
- The post-cholecystectomy symptoms are usually the associated "non-biliary colic"
- The older "larger" (↑ BMI), immunosuppressed person with atypical symptoms or fewer of unknown origin presentations (sepsis)
 - Perform abdominal ultrasound so as not to misdiagnose gallbladder disease

➤ Diagnostics imaging

	<u>Sensitivity</u>	
○ Abdominal ultrasound	95%	– False-negative ▪ ↑ BMI
○ Endoscopic ultrasound	94 - 98%	– Especially useful when cholecystolithiasis is suspected but ultrasound is negative
○ MRI		– If ultrasounds are negative, but clinical suspicion is high for gallstone disease
○ Complications		
– Gallbladder	▪ Acute cholecystitis ▪ Gangrene ▪ Empyema ▪ Perforation ▪ Bilioenteric fistula, ileus	
– Duct	▪ Choledocholithiasis ▪ Cholangitis	
– Pancreas	▪ Acute biliary pancreatitis	

Abbreviations: ESWL, extracoporal shock wave lithotripsy; UDCA, ursodeoxycholic acid

Do the Math

- Give why dissolution (litholysis) UDCA of small radiopaque (non-clacified) gallstone in a functioning glaabladder, is not recommended:
 - 6 mon of UDCA dissolves stones in 2/3 patients
 - High recurrence rate of symptomatic stones
 - 5 yr ~50%
 - 10 yr ~70%



Asymptomatic Gallstones

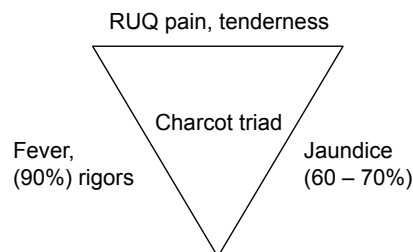
- Diagnosis
 - No routine cholecystectomy or bile acid litholysis / extracorporeal shockwave lithotripsy (ESWL)
 - This includes stones found during unrelated surgery
 - Yes
 - Hereditary spherocytosis
 - Sickle cell disease
 - Porcelain gallbladder
- Preventive therapy
 - Healthy diet and regular activity
 - UDCA
 - Not recommended, including for current CBD stones
 - Exception: UDCA
 - Rapid weight loss, e.g., bariatric surgery
 - Long-term use of somatostatin / octreotide

Acute Cholecystitis

- Demography
 - ~15% of population has asymptomatic gallstones $\xrightarrow{20\%}$ symptomatic $\xrightarrow{10\%}$ acute cholangitis
 - ~50% patients with acute cholecystitis will have had a previous episode of biliary colic

Clinical signs

- RUQ-pain
 - Severe
 - > 5 hr duration
 - Fever
 - Nausea / vomiting
 - Tenderness (Murph sign)



Diagnosis

- Clinical suspicion
 - Fever, severe pain located in the right upper abdominal quadrant lasting for several hours, and right upper abdominal pain and tenderness on palpation (Murphy's sign)
- ↓
- Abdominal ultrasound
 - ↓
 - Broad spectrum antibiotics for cholangitis, sepsis, abscess, perforation
 - ↓
 - Early (within 72 hr) laparoscopic cholecystectomy



➤ Laboratory

- ↑ WBC, ↑ ALT / AST, ↑ CRP

➤ Diagnostic imaging

- Abdominal ultrasound

- Give the findings on abdominal ultrasound of acute cholecystitis.

- Gallstones
- Gallbladder
 - Distended
 - Thick wall (> 4 mm)
 - Precholecystic fluid
- Positive Murphy sign with presence of ultrasound over gallbladder
- Performance characteristics

Positive Predictive Value (PPV)

- Stones plus	}	92%	}	95%
- Thick wall or				
- Positive ultrasound,				
Murphy sign				

- Nuclear imaging scan (Tc – HIDA)
 - Non-filling of gallbladder
 - Stones are not demonstrated
- Specificity
 - MR = Tc – HIDA = abdominal ultrasound

➤ Treatment

- Treatment predisposing factors
- Pain control
 - NSAIDs / acetaminophen
 - Anticholinergics
 - Opiod analgesics
 - Nitroglycerin
- Cholecystectomy within 24 hr in selected patients***
- Exclude cholangitis
- Antibiotics if
 - Acute cholangitis
 - Abscess
 - Bacteremia / sepsis
 - perforation
- *** cholecystectomy usually necessary for biliary colic if
 - ≥ 70 yr
 - Diabetes mellitus
 - Distended gallbladder on admission
 - Persistent ↑ HR, ↑ WBC



- IV fluids
 - Antibiotics for immunosuppressed persons with
 - Acute cholangitis
 - Abscess perforation
 - Bacteremia / sepsis
 - Empirical antibiotic coverage against aerobic gram-negative bacteremia and anaerobic bacteria
 - Biliary decompression of patient not responding to analgesics, IV fluids and antibiotics
 - ↓
 - ERCP with sphincterotomy
 - ↓ if contraindication to sphincterotomy
 - ERCP, stenting, stone removal or
 - Percutaneous drainage
 - ↓
 - Nasobiliary drain or
 - Endoprosthesis for large / multiple stones coagulation abnormality
 - Cholecystectomy
 - Early (within 24 hr) if:
 - Older ≥ 70
 - Serious condition
 - Diabetes melitus
 - Distended gallbladder
 - $\uparrow$ HR, $\uparrow$ WBC
 - Late (after 6 wk)
- $\downarrow$ rate of conversion from laparoscopic to open cholecystectomy
 - $\downarrow$ length of stay (LOS) in hospital
 - Note: no difference in rate of serious complications in lap' vs opn cholecystectomy

Laboratory Alert

In the patient with acute cholangitis, the blood cultures do not reflect the organisms which are cultured in the bile.

SO YOU WANT TO BE A GASTROENTROLOGIST!

- Give why cholecystectomy is performed for acute cholecystitis early (< 1 wk) or late (> 6 wk), but not between 1 to 6 wk.
 - There is $\uparrow$ risk of death from laparoscopic cholecystectomy performed for acute cholecystitis when performed 1 to 6 wk after acute cholecystitis, as compared to < 1 or > 6 wk.



Endoscopic Tips

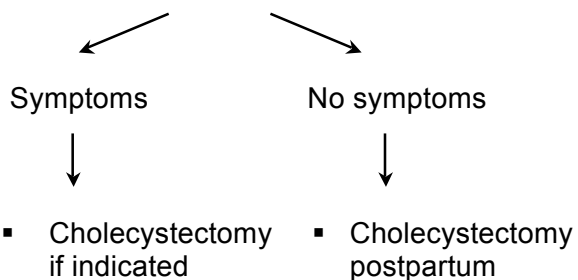
- For acute cholangitis, perform sphincterotomy with ERCP, even if stones are not found in the CBD.
- When doing an ERCP for acute cholangitis, cannulate the CBD and drain stones before injecting contrast dye.

Acute Cholangitis

- Clinical suspicion
 - Fever and history of chills, with abdominal pain and/or jaundice, ↑ white blood cell, ↑ C-reactive protein and ↑ liver biochemical tests
- ↓
- Abdominal ultrasound
- ↓
- IV fluids
- Broad spectrum antibiotics IV
- ↓
- Drain CBD
 - ERCP sphincterotomy or stenting if contraindications for sphincterotomy
- ↓
- Percutaneous drainage of CBD if failed / contraindicated ERCP

Stones in gallbladder plus BD

- ERCP and BD stone extraction, then
- Early (< 72 hr) cholecystectomy
- Pregnancy plus BD stones
 - ERCP plus stone extraction (minimum radiation exposure time)
 - Bile duct stones cleared



Symptomatic Gallstones Drug Pregnancy

➤ Demography

- 5% of pregnant women develop gallstones or sludge, but
 - Only 1% develop biliary pain
 - Symptom
 - T₁, 92%, T₂, 64%, T₃, 44% $\xrightarrow{1/3}$ complications
 - Of these who have asymptomatic gallstones during pregnancy, many require cholecystectomy

➤ Treatment

- If necessary, perform cholecystectomy in T2 (second trimester) as this is safest trimester for surgery.
- ERCP safe to perform in pregnancy, but risk of post ERCP pancreatitis is higher.

Elective / Prophylactic Cholecystectomy

- Calcified (“porcelain”) gallbladders
 - With spotty (not homogeneous) calcification
- Gallbladder polyps
 - With PSC
 - All single polyps considered to be adenomas with malignant potential → cholecystectomy
 - No PSC
 - ≥ 1 cm (50% of these are malignant), or
 - Polyps 6 - 10 mm
 - Polyps which are enlarging may be considered for surgical removal by cholecystectomy
- 2 year after heart transplantation
- Not indicated in asymptomatic patients (even with diabetes mellitus)
- At the time of splenectomy for person with hereditary **sphenocytosis**
- At the time of abdominal surgery for other reasons for persons with sickle cell disease

Abbreviation: PSC, primary sclerosing cholangitis

Practice Caution

- In the patient with PSC who is therefore at ↑ risk of gallbladder cancer, if no gallbladder polyps are seen on abdominal ultrasound (AUS), perform endoscopic ultrasound (EUS) because of its greater sensitivity

	Sensitivity
– EUS	87 – 97%
– AUS	52 – 76%



Interesting, but don't risk it!

- Number of gallbladder polyps
 - Adenoma, 1
 - Cholesterol polyps, ≥ 1
- Doppler (colour, duplex) ultrasound
 - Adenoma may be seen to have a blood vessel at the base of the polyp
- In a patient with multiple gallbladder polyps or polyps < 10 mm and a negative Doppler ultrasound, don't take the risk of misdiagnosing a premalignant/malignant lesion.

Cholecystectomy

- Most (93%) are started as laparoscopic cholecystectomy
 - Conversion from laparoscopic to open cholecystectomy is $\sim 7\%$
 - Start with lap' chole' for cirrhotic patients (Child-Pugh A or B, MELD score < 13)
 - Open cholecystectomy or endoscopic cholangiography (ERC) stent
- Complications

- Bile leak	}	$\sim 1\%$
- Infection (wound)		
- Pancreatitis	}	$\sim 0.3\%$
- Bleeding		
- Options for high risk surgical patients with acute cholecystitis
 - Percutaneous cholecystostomy clinical benefit followed by cholecystectomy
 - Nasobiliary drainage
 - Transpapillary stent
 - ERCP with sphincterotomy

Injury to the Bile Duct

➤ Definition

- Any damage to the bile duct that may have a negative impact on the patient

➤ Demography

- With cholecystectomy
 - Open 0.5%
 - Laparoscopic 0.04 - 1.5%

➤ Risk factors

○ Congenital / surgical anatomical abnormalities	}	$\uparrow$ mortality rate	
○ Impacted stones			- Cystic duct
			- Hartmann pouch
○ Inflammation			
○ Mirizzi syndrome			



➤ Diagnostic imaging

Contrast (gadoteric acid disodium) – SENS > 75%
MRCP – SPEC ~ 100%

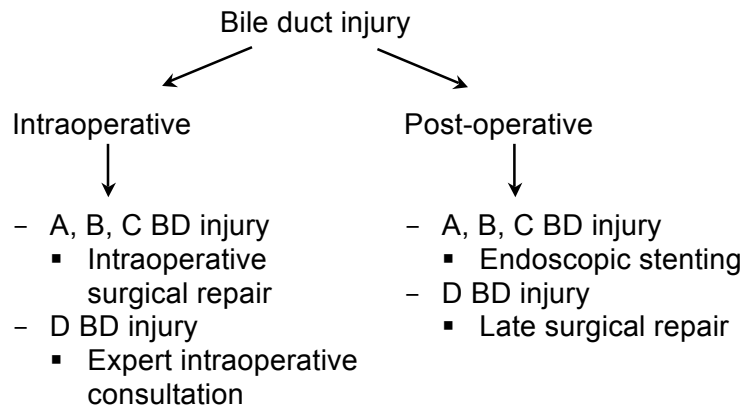
ERCP



Intraoperative cholangiography

➤ Classification (Amsterdam) of bile duct injuries

A	CD / aberrant duct	○ Leakage	– Reclosure
B	CBD	○ Leakage +/- stricture	– Primary surgical repair (choledochodochal repair), or – Subhepatic drainage, or
C		○ Stricture, no leakage	– ERCP stenting, dilation
D		○ Transection	– Primary repair (reconstruction 6-8 wk after injury) – Roux-en-Y hepaticojejunostomy



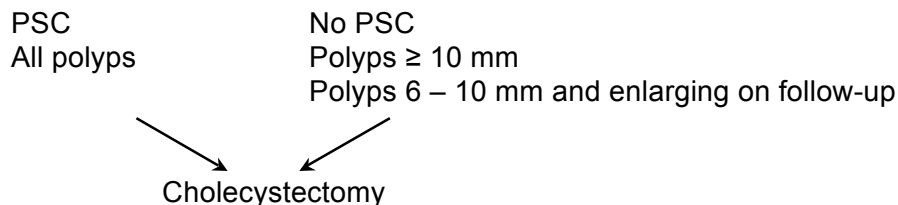
Abbreviations: CBD, common bile duct; CD, cystic duct; ERCP, endoscopic retrograde cholangiopancreatography

Biliary Symptoms which Persist After Cholecystectomy (Post-cholecystectomy Syndrome)

- Recurrent bile duct stones
 - Rule out ABCB4 gene mutation leading to LPAC
 - Sludge / microlithiasis
- Other disorders
 - Cautious consideration of ERCP / sphincterotomy if biliary pain, ↑ cholestatic blood test, ↑ sphincter of Oddi pressure



GALLBLADDER POLYPS



Abbreviation: PSC, primary biliary sclerosis

BILE DUCT STONE DISORDERS

Cholelithiasis

- Demography
 - Of patients with cholelithiasis, ~ 10% have choledocholithiasis
 - Migration from gallbladder
 - Primary stones formed de novo in CHD / CBD due to stasis / dilation
- Clinical
 - 90% are symptomatic
 - Acute biliary pain
 - Acute cholangitis
 - Cholangitis
 - Acute pancreatitis

Abbreviations: CBD, common bile duct; CHD, common hepatic duct

Laboratory

< 72 hr	–	↑ ALT, ↑ AST
> 72 hr	–	↑ Bilirubin, AP, GGT
	▪	Positive predictive value (PPV) < 50%

CBD normal on ultrasound and biochemical tests normal

- ↓↓↓ risk of CBD stones (↑ negative predictive value [NPV])

- In 1/3 of persons with CBD stones, serum bilirubin is ↑
- Of these people, the concentration of serum bilirubin has only a modest specificity for Choledocholithiasis

Serum Bilirubin Concentration		Specificity
μmol/L	mg/dL	
– 29	1.7	60%
– 68	4.0	75%



➤ Diagnosis

- Clinical suspicion
 - Jaundice, acute cholangitis or acute pancreatitis
- ↓
- Abdominal ultrasound
- Liver biochemistry
- ↓
- EUS, MRCP, ERCP (intermediate probability)
- ↓
- ERCP with stone extraction
- ↓
- Failed extraction
 - Lithotripsy (ECSW, EHL, LL)
 - Laparoscopic bile duct exploration plus cholecystectomy
 - Roux-en-Y Percutaneous or endoscopic balloon-assisted extraction
- Intraoperative diagnosis of BD stones
 - Removal BD exploration
 - Transcystic removal intraoperative “ERCP” with stone removal
- Cholecystectomy
- Post-cholecystectomy diagnosis of BD stones
 - ERCP plus stones extraction

➤ Diagnostic imaging

- Symptomatic intrahepatic bile duct dilation and stones → secondary biliary cirrhosis
 - Liver transplantation
- Abdominal ultrasound

	<u>Sensitivity</u>
– Cholelithiasis	95%
– Choledocholithiasis	75%
- ↓
- EUS or MRCP

	<u>Sensitivity</u>	<u>Specificity</u>
▪ EUS	95%	97%
▪ MRCP	93%	96%

Recurrent bile duct stones in young person suspect ABCB4 mutation producing low phospholipid-associated cholelithiasis (LPAC).



➤ Treatment

- Gallbladder stones, symptomatic
 - Cholecystectomy
- Cholecystectomy during same hospital admission if:
 - Mild biliary pancreatitis (once pain resolves) and
 - Once amylase / lipase concentrations are near normal (usually ≤ 72 hr)
 - Severe biliary pancreatitis = surgery after 6 wk when peripancreatic fluid collection has resolved
- ~ 10% of patients with symptomatic cholelithiasis develop cholelithiasis →
 - Biliary pain
 - Biliary obstruction (jaundice)
 - Pancreatitis
 - Cholangitis

↓

 - ERCP, sphincterotomy and stone extraction or
 - Balloon dilation plus extraction
- Stones in both gallbladder and bile duct → preoperative ERCP, then cholecystomy plus removal of CBD stones
 - Intraoperative ERCP
 - Transcystic stone extraction
 - CBD exploration

or

 - Cholecystectomy plus post-operative ERCP
- After surgical bile duct exploration
 - Low risk
 - Primary closure
 - High risk
 - Acute cholangitis
 - CBD stones
 - Recurrent
 - Multiple

↓

 - T-tube drainage, or
 - Choledochoduodenostomy

Intrahepatic Bile Duct Stones (Hepatolithiasis)

➤ Causes / associations

- Bile duct
 - Strictures / injury
 - Sclerosing cholangitis
 - Oriental cholangitis

➤ Complications

- Abscess of liver
- Atrophy
 - Lobe / segment
- Biliary cirrhosis, secondary
- Cholangiocarcinoma



➤ Clinical

- ~12% in 4 yr become symptomatic



- Biliary colic
- Bile duct obstruction (jaundice)
- Cholangitis
- Abscess (liver)
- Cholangiocarcinoma

➤ Diagnosis

Abdominal ultrasound



Multidisciplinary team decision

➤ Diagnostic imaging

- MRCP is test of choice for hepatolithiasis, as compared with ERCP
- Sensitivity to detect intrahepatic bile duct stones
 - Obstruction proximal / outside bile ducts
 - Strictures

➤ Treatment

- Partial hepatectomy
 - Cholangiocopic lithotripsy (CSL)
 - Peroral (POCSL)
 - Percutaneous, transhepatic (PT CSL)
- } > 80% complete removal of stones

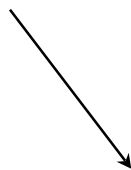
Acute Biliary Pancreatitis

- Clinical suspicion
 - Upper abdominal pain and altered pancreatic and liver biochemical tests in patients with gallbladder and or common bile duct stones

- Mild symptoms



Endoscopic ultrasound



Cholecystectomy

- Severe symptoms

- Cholangitis
- BD obstruction



- Broad spectrum antibiotics and
- Early (< 24 hr) ERCP, sphincterotomy and stone extraction



PANCREAS



ACUTE PANCREATITIS (AP): ACG / AGA Guidelines

Abbreviations: ACG, American College of Gastroenterology; AGA, American Gastroenterology Associations

Tenner S, et al. Am J Gastroenterol 2013; 108: 1400-15; and Forsmark CE and Baillie J. Gastroenterology 2017; 132: 2022-44.

Please also see AGA Institute Technical Review Gastroenterology 2007; 132: 2022-2044.

- Suspect diagnosis
 - Abdominal pain
 - ↑ serum lipase / amylase > 3 x ULN
-/+
 - Abnormal abdominal ultrasound
 - ↓ - Lack of improvement in 48-72 hr
 - ↓ - Diagnosis unclear
- Diagnostic imaging
 - CECT / MRI
 - MRCP / EUS if suspected choledocholithiasis
 - ERCP within 24 hr if
 - AP plus biliary obstruction (e.g., acute cholangitis)
 - ↑ risk of post-ERCP pancreatitis
 - ↓
- Risk stratification
 - Presentation
 - SIRS
 - Heart rate (HR) > 90 bpm
 - Temperature > 38°C, or < 36°C
 - Respiratory rate (RR) > 20/min, or PaCO₂ < 32 mmHg
 - WBC > 12,000 cells/μL, or < 4000 cells/μL, or > 10% bands
 - Predictors of disease
 - Ranson criteria
 - Atlanta / Atlanta revised (shock; lung and kidney failure; GI bleeding; DIC; hypocalcemia)
 - APACHE II / III
 - Glasgow criteria
 - CT scan
 - Balthazar CT score
 - CT severity
 - Simple routine measures
 - Blood urea nitrogen (BUN)
 - Of multiple routine measurements, the BUN gives the best estimate of predicting 24 and 48 hr mortality
 - For every 5 mg/dL increase in BUN during the first 24 hr, the age- and gender-adjust (odd ratio) for mortality also increases by 2.2.
 - Hematocrit (Hct)
 - > 44% in admission and at 24 hr has a sensitivity to predict organ failure of 72% and 94%, respectively
 - Pancreatic necrosis / organ failure

- Special considerations re: etiology
 - < 30 yr old, if no alcohol or gallstone
 - Genetic testing for gallstones
 - > 40 yr old, possibly caused by pancreatic cancer (MRI-PP)
 - Measure fasting serum triglyceride



➤ Treatment

- ICU admission if organ failure
- Analgesic



- IV fluid resuscitation (250-500 mL per hr, isotonic crystalloid solution or Ringer's lactate solution for 12-24 hr, unless severe heart / kidney disease)



- End-point: Reduce the elevated BUN



- Antibiotics
 - Extrapancreatic infection
 - Infected necrosis
 - FNA - Culture directed, or empiric antibiotics



- Metronidazole
- Quinolones
- Carbapenems

- Nutrition

Severe AP

Mild AP

- Enteral feeding by NG or NJ tube
- Clear fluids or low-solid diet

- Cholecystectomy (chole')
 - Mild AP - before hospital discharge
 - Necrotizing biliary AP-delay chole' ~ 6 wk until necrosis stabilizes

- Symptoms
 - Necrosectomy
- No symptoms
 - ↓ drainage in 4 wk
 - Endoscopic
 - Radiologic
 - Surgical

- Pseudocysts / necrosis (pancreatic, extrapancreatic)
 - No symptoms: follow up
 - Symptoms: drainage after 4 wk (to achieve walled-off necrosis [WON])

Abbreviations: AP, acute pancreatitis; BUN, blood urea nitrogen; CECT, contrast enhanced CT scan; DIC, disseminated intravascular coagulopathy; ERCP, endoscopic retrograde cholangiopancreatogram; FNA, fine needle aspiration; MRCP, magnetic resonance cholangiopancreatogram; MRI-pp, MRI pancreatic protocol; NG, nasogastric; NJ, nasojejunal; NSAID, non-steroidal anti-inflammatory drug; SIRS, severe inflammatory response syndrome; ULN, upper limit of normal

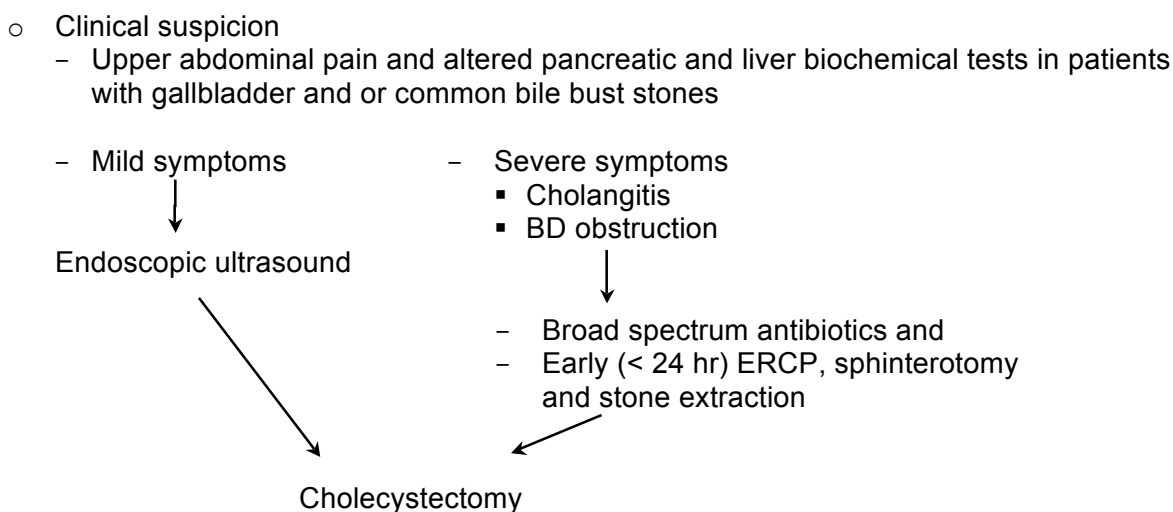


➤ Greater Specificity of Serum Lipase Versus Amylase

	Lipase	Amylase
○ Pancreatic and biliary tree	+	+
○ Intestinal	+	+
– Obstruction		
– Ischemia		
○ Acute appendicitis	+	+
○ Pregnancy	+	+
○ Renal failure	+	+
○ CNS	-	+
– Head trauma, plus intracranial bleeding		
○ Salivary gland	-	+
– Parotitis		
○ Lung	-	+
– Carcinoma		
○ Ovary	-	+
– Cyst, cancer		
○ Endocrine	-	+
– Diabetic ketoacidosis		
– Macroamylasemia		
○ HIV infection	-	+

Note: Serum lipase has a longer half-life ($T_{1/2}$) than does amylase, and is less affected by non-pancreatic / non-gastrointestinal disorders.

Acute Biliary Pancreatitis



ROLE OF ENDOSCOPY IN BENIGN PANCREATIC DISEASE: ASGE Guidelines

Abbreviation: ASGE, American Society for Gastrointestinal Endoscopy

Chanrasekhara V, et al. Gastrointestinal Endoscopy 2015; 82: 203-247.

Acute Pancreatitis

- Give the role of diagnostic imaging to determine cause of first episode of pancreatitis.
 - Gallbladder sludge, microlithiasis
 - Bile ducts choledocholithiasis
 - Pancreas
 - Inherited
 - Inflammatory
 - Infiltration
 - Functional
 - Pancreas divisum
 - Acute exacerbation of chronic pancreatitis
 - Tumour, crypts
 - Sphincter of Oddi dysfunction

Pancreas Divisum

- Give the diagnostic procedure which is optimal for the diagnosis of PD.
 - EUS superior to CT or MRI
 - Performance characteristics of CT/MRI is superior when secretin is given
 - ERCP for treatment papillotomy of minor duct or stenting of the minor papilla (early improvement of symptoms, 60%; recurrence of 50% within 6 mon)

Sphincter of Oddi Dysfunction (SOD)

- Types
 - Type 2 SOD
 - SOD manometry + ERCP sphincteropathy, or
 - Empirical ERCP sphincterotomy
 - Benefit ~ 70% of idiopathic acute pancreatitis
 - Type 3 SOD
 - No benefit of biliary +/- pancreatic sphincterotomy
- } Biliary +/- pancreatic duct (similar symptom response)



AUTOIMMUNE PANCREATITIS (AIP)

Hart PA and Chari ST. Gastroenterology 2015; 149; 39-51.

➤ Types

- 1
 - Lymphoplasmacytic sclerosing pancreatitis ↑ IgG4+ serum, plasma cells
 - Histopathology
 - Fibrosis
 - Obliterative venulitis
- 2
 - Ideopathic duct-centric pancreatitis
 - Histopathology
 - Granulocyte epithelial lesion N / ↓ IgG4 serum, plasma cells
 - Associated with IBD

➤ Diagnostic imaging

- CT not typical for AIP → ERP
 - PD strictures
 - Multiple
 - Long
 - Narrow
 - CBD strictures in ~ 40%
 - < 5 mm dilation
 - Side branches
- Clinical
 - Features suggestive of IgG4-associated biliary structures → ERCP
- EUS
 - Pancreatic
 - ↑ size
 - Hypoechoic axis
 - BD wall ↑ thickness
 - Peripancreatic
 - Focal hyperechoic areas

➤ Biopsies

- Endobiliary
- Ampulla
 - Performance characteristics for AIP
 - Sensitivity ~ 75%
 - Specificity ~ 95%
- EUS-guided FNA
 - Gives diagnosis of AIP in ~ 40%
 - False-negative biopsies do not exclude pancreatic duct adenocarcinoma

➤ Treatment

- Corticosteroids
 - ↓ Failure and biliary strictures
 - Stenting

Abbreviations: BD, bile duct; CBD, common bile duct; ERCP, endoscopic retrograde cholangiopancreatogram; ERP, endoscopic retrograde pancreatogram; EUS, endoscopic ultrasound; FNA, fine needle aspiration; PD, pancreatic duct



CHRONIC PANCREATITIS (CP): APA GUIDELINES

Abbreviation: APA, American Pancreatic Association

Conwell DL, et al. Pancreas 2014; 43: 1143-1162.

➤ Demography

	per 10 ⁵	
	Males	Females
○ Incidence	8	4
○ Prevalence	50	25

➤ Causes / associations

- There are numerous methods used to classify the etiology and risk factors for chronic pancreatitis
 - Shown below are the classification systems proposed by the American Pancreatic Association Practice Guidelines (Conwell DL, et al. Pancreas 2014; 43: 1143-1162)

Classification Systems for Etiology and Risk Factors for

❖ Traditional

- Alcohol, idiopathic, hereditary, obstructive, hyperlipidemia

❖ TIGAR-O

- Toxic-metabolic: alcohol, tobacco smoking, hypercalcemia, hyperlipidemia, chronic renal failure, medications, toxins
- Idiopathic: early onset, late onset, tropical
- Genetic mutations: PRSS1, CFTR, SPINK1, others
- Autoimmune: isolated, syndromic
- Recurrent and severe AP-associated CP: postnecrotic (severe AP), vascular disease / ischemic, post-irradiation
- Obstructive: pancreas divisum, sphincter of Oddi disorders, duct obstruction (e.g., tumour), post-traumatic pancreatic duct scars

❖ “MANNHEIM”

- **M** indicates multiple risk factors including
 - **A**lcohol consumption: excessive (>80 g/d), increased (20-80 g/d), moderate (< 20 g/d)
 - **N**icotine consumption
 - **N**utritional factors: high calorie proportion of fat and protein, hyperlipidemia
 - **H**ereditary factors: hereditary, familial, idiopathic (early onset, late onset), tropical
 - **E**fferent duct factors: pancreas divisum, annular pancreas and other congenital abnormalities of the pancreas, pancreatic duct obstruction (e.g., tumours), post-traumatic pancreatic duct scar, sphincter of Oddi dysfunction
 - **I**mmunological factors: autoimmune pancreatitis
 - **M**iscellaneous and rare metabolic disorders: hypercalcemia, hyperparathyroidism, chronic renal failure, drugs, toxins



➤ Genetics

Mutations associated with CP

Gene Name	Pathophysiology	Unique Effect on Modifying
Calcium sensireceptor (CASR)	$\uparrow \text{Ca}^{2+} \rightarrow$ - $\uparrow$ trypsin activation - $\downarrow$ trypsin degradation	
Cystic fibrosis transmembrane conductance receptor (CFTR)	$\uparrow \text{Cl}^- / \text{H}_2\text{O}$ secretion $\rightarrow$ trypsinogen remains in ducts $\rightarrow \uparrow$ trypsin	Idiopathic pancreatitis
Chymotrypsin RC (CTRC)	$\downarrow$ trypsin degradation	Tropical pancreatitis
Cationic trypsinogen (PRSS1)	$\uparrow$ trypsinogen activation $\downarrow$ trypsin degradation	Penetrance for AP (80%) and for CP (40%)
Pancreatic secretory trypsin inhibitor (SPINK1)	$\downarrow$ trypsin degradation	Non-alcoholic CP

Abbreviations: AP, acute pancreatitis; Ca^{2+} , extracellular ionized calcium; CP, chronic pancreatitis

➤ Laboratory

❖ Pancreatic Function Testing

- Indirect
 - Serum trypsin < 20 pg/dL
 - 72 hr quantitative stool fat collection > 7 d/d
 - Fecal fat droplets > 6 /hpf
 - Fecal elastase < 50 $\mu\text{g}/\text{dL}$
- Direct
 - Lundt meal stimulation test
 - Endoscopic pancreatic functional test

} with Dreiling tube

- Detects 30% pancreatic damage, so more sensitive than US, CT, MRI or indirect PTT



- Ducts
 - Main pancreatic duct
 - Dilation (main pancreatic duct)
 - Irregular
 - Margins hyperechoic, +/- honey combing
 - Calculi

Investigation	Histological Correlates	
	Parenchyma	Ducts
○ MRI - Most useful early ▪ Atrophy (54%) +/- inflammation ▪ Fibrosis		▪ Dilation of PDs - Boarding ▪ MPD ▪ SBPs (50%)
○ CT - Complications ▪ Pseudocysts ▪ Portoslenic vein thrombosis	▪ Fluid collections (30%) ▪ Focal enlargement (30%)	▪ Calcifications (dystrophic intraductal)
○ US	▪ Other cancer diagnosis	▪ Bile duct dilation (29%)
○ EUS	▪ Hyperechoic foci, with shadowing ▪ Hyperechoic strands ▪ Lobular contour cysts (honeycombing) ▪ Focal fibrosis ▪ Bridging fibrosis ▪ Interlobular fibrosis ▪ Cyst / pseudocyst	▪ Main duct dilation, mm ▪ Duct irregularity ▪ Hyperechoic margins ▪ Visible side branches ▪ Stones ▪ > 3 head, > 2 body, > 1 tail ▪ Focal dilation / narrowing - Periductal fibrosis - Side branch dilation - Calcified stones
○ CT - Calcifications do not correlate with exocrine function - The pancreas in the patient with chronic pancreatitis may be normal		
○ MRI - Duct changes are specific for CP - Signal intensity may change before duct abnormalities - Secretin infusion may accentuate early ductal changes parenchyma ▪ ↑ fat-suppressed T1-weighted images ▪ ↓ / slower enhancement with gadolinium in early CP		

Abbreviations: EUS, endoscopic ultrasound; MPD, main pancreatic duct; PD, pancreatic ducts; SBRs, side branch radicals



- Endoscopic ultrasound (EUS)
- Give the EUS criteria for CP.
 - < 2 not CP
 - ≥ 5 CP
- Poor performance characteristics for early CP
- Great interobserver variability (low kappa value)
- Endoscopic retrograde cholangiopancreatogram (ERCP)
 - Indication
 - Only when diagnosis of CP unclear after CT / MRI or after pancreatic function testing

Modified **MannHeim Imaging Grade** for Pancreatic Morphology

	(I) Equivocal	(II) Mild	(III) Moderate	(IV) Marked
❖ US, CT, MRI	1 of the following	≥ 2	≥ 2	≥ 2 plus
○ Duct – MPD ▪ ↑ size, 2 - 4 mm ▪ ↑ echogenicity – Irregular duct ○ Parenchyma – Enlarged – Heterogeneous – Cavities (< 10 mm) – Irregular contour (head / body) – Focal acute pancreatitis				– Filling defects / stones in ducts – Obstruction – Stricture – Irregularity
				++
				> 10 mm
❖ EUS	0 - 2	3 - 4	> 5	
❖ MRCP / ERCP				
○ Abnormal side-branch changes	> 3	> 3	> 3	– Obstruction – Filling defects
○ Abnormal MPD				– Severely MPD dilated irregular
➤ Endoscopic pancreatic function testing (ePFT)				
○ EGD +secretin injection, with aspiration of duodenal contents at 15, 30, 45 and 60 min and demonstration of peak HCO ₃ < 80 mEq/L				
– A HCO ₃ - in ePFT > 80 mEq/L excludes chronic pancreatitis (CP), due to the high negative predictive value of this test				



➤ **Rosemount Criteria** for EUS features of Chronic Pancreatitis

Note: Perform EUS ≥ 4 wk after episode if acute pancreatitis

Criteria	Pancreatic Parenchyma	Main Pancreatic Duct (MPD)
Major		
A	○ Hyperechoic foci – Shadowing	▪ Calculi
B	○ Lobularity – Honeycombing	
Minor	○ Hyperechoic foci – No shadowing – Stranding ○ Lobularity ○ No honeycombing ○ Cysts	▪ Dilation ≥ 3 side branches ▪ Hyperechoic ▪ Irregular ▪ Dilation – Body > 3.5 mm – Tail > 1.5 mm

Adapted from: ASGE Guidelines. Gastrointestinal Endoscopy 2015; 82: 103-214, Table 2.

➤ Problems with Rosemount Classification

- Cannot be done < 4 wk after acute pancreatitis
 - Large variability
 - Age
 - Male gender
 - Alcohol
 - Tobacco
 - $\uparrow$ BMI (obesity)
 - Large inter-observer agreement
 - Doesn't prevent need for FNA
- The patient with chronic pancreatitis (CP) have a $> 2\%$ risk of developing pancreatic ductal adenocarcinoma. If the CT scan is performed, it must be a pancreatic protocol (triple-phase). Give the sensitivity of adding FNA to EUS to diagnose PDA.
 - EUS $< 75\%$
 - EUS + FNA $\sim 85\%$



➤ Pathology

- Atrophy of exocrine tissue +/- chronic inflammation
 - Perilobular, intralobular
- Fibrosis
 - Focal, patchy, diffuse
 - Progressive

➤ Treatment

- Histopathology
- ↓ acinar cells (destruction of pancreatic parenchyma)
- Chronic inflammation
- Fibrosis

Hereditary Pancreatic Cancer

- Mutation carriers from hereditary syndromes associated with risk of pancreatic cancer
 - Peutz-Jeghers syndrome
 - Hereditary pancreatitis
 - Mutation carriers of BRAC1 / 2, PALB2, ATM or LS
 - First-degree relatives with pancreatic cancer
 - Familial atypical multiple myeloma and mole (FAMMM) syndrome
 - Pancreatic cysts in person under surveillance for pancreatic cancer in one of the above cancer-prone groups
- EUS / MRI q 1 yr starting at
 - 50 yr, or
 - 10 yr less than the earliest age of pancreatic carrier in the family

Source: Giardiello FM, et al. Am J Gastroenterol 2014; 109: 1159-1179; Ladabaum U, et al. Gastroenterology 2015; 149: 783-813; Rubenstein JH, et al. Gastroenterology 2015; 149: 777-782; Syngal S, et al. Am J Gastroenterol 2015; 110: 223-262

Pancreatic Duct Strictures

➤ Endoscopic methods

- To obtain tissue for diagnosis
 - Brushing → Cytology
 - Confocal → Endomicroscopy
- To dilate before stenting
 - Efficacy to ↓ pain (no intraductal stones) ~ 75%
 - Single or multiple stents
 - 3 stents, pain relief ~ 85%



- EUS-guided drainage
 - Anterograde
 - Duct puncture, transmural drainage
 - Transpapillary stent
 - Retrograde
 - Transpapillary drainage
 - Symptom relief
 - Technical success ~ 75%
 - In persons with technical success
 - Early ↓ pain ~ 70% to 80%
 - Late benefit ~ 20%

Pancreatic Stones

- Give the management of pancreatic pain.
 - Pancreaticolithiasis
 - ESWL
 - Extracorporal shock wave lithotripsy before removal of stones (fragments) by ERCP
 - Mini-lithotripter device is available
 - Endotherapy of strictures
 - ↓ pain in 2 / 3 of patients
 - Short-term ~ 80%
 - Long-term ~ 45%
 - Endotherapy alone is as effective as endotherapy +ESWL, although better results of ESWL clearance of MPD performed within < 2 days (82% vs 14%)
 - In patients with chronic pancreatitis and obstruction of pancreatic duct, surgery was superior to endoscopic therapy for the long-term (5-yr) complete but not partial pain relief

Pain Relief	Surgery	Endoscopic Therapy	
- Complete	34 - 37%	49 - 52%	} About half of these patients later require pancreatic surgery
- Partial	14 - 15%	51 - 52%	

Note: If operative intervention is required, the mortality rate is ~ 2%

- Give the factors which predict the success of endoscopic therapy relieving pancreatic pain.
 - Patient
 - Short duration of pancreatic disease
 - Lack of use of alcohol / cigarettes
 - Pathology
 - Disease in head of pancreas
 - No stricture
 - Complete PD clearance with the first therapeutic ERCP



Post-ERCP Complications: ASGE Guidelines

Abbreviation: ASGE, American Society for Gastrointestinal Endoscopy

Anderson MA, et al. Gastrointestinal Endoscopy 2012; 75: 467-473.

➤ Demography

- Pancreatitis
 - “Biochemical” (↑ lipase / amylase), ~ 75%
 - Clinical ~4%
- Bleeding
 - Mild, ~ 1%
 - Severe < 0.3%
 - Risk of needing ≥ 5 U PRBC, surgery or angiography
- Perforation, ~ 0.5%
 - Overall < 1%
- Cholangitis, < 1%
 - ERCP for inoperable obstruction of the hilum
 - Contrast before stenting
 - Air 3%
 - Iodine ~ 25%
- Cholecystitis < 0.5%
- Cardiopulmonary complications
 - Incidence < 1%
 - Mortality (1/1000)

Post-ERCP Pancreatitis (PEP)

➤ Diagnosis

- Sensitivity to detect most pancreaticobiliary conditions ERCP = EUS = MRCP
 - Only ERCP has risk of biochemical / clinical pancreatitis
- Consider using EUS / MRCP as diagnostic tools, and ERCP for therapy

➤ Risk factors

- Give the risk factors for post-ERCP pancreatitis (PEP).
 - Patient
 - Past history of post-ERCP pancreatitis
 - Young patient
 - SOD as the indication for ERCP
 - Normal serum bilirubin concentration
 - Procedure

– Pancreatic duct ▪ Injection ▪ Sphincterotomy ▪ Brush cytology ▪ Wire manipulation ▪ Ampullectomy	– Bile duct ▪ Balloon dilation ▪ Difficult cannulation ▪ Cannulation of BD not performed with wire-guidance



➤ Prevention

- Give suppository of diclofenac or indomethacin just before or after ERCP
 - ↓ risk of post-ERCP pancreatitis
- Temporary stenting of PD may ↓ risk of PEP for many of the PEP risk factors

❖ Post-ERCP Bleeding

➤ Types

- Site
 - Intraluminal
 - Hematomas
 - Liver
 - Spleen
 - Timing
 - Early (observed)
 - Late (delayed up to 2 wk)
- } Early bleeding predicts the possibility of delayed bleeding

➤ Risk factors

- Give the risk factors for post-ERCP bleeding.
 - Patient
 - Coagulopathy
 - Anticoagulants within 72 hr of ERCP / sphincterotomy
 - ↑ serum bilirubin
 - Condition (indications)
 - Acute cholangitis
 - Stenosis of papilla
 - Precut sphincterotomy
 - Physician
 - Non-expert / inexperienced

Perforation

➤ Types

- Site
 - Anywhere
 - Guidance-associated
 - Periapillary
 - During sphincterotomy
 - Remote from papilla
 - Luminal perforation

➤ Risk factors

- Precut sphincterotomy
- Malignancy



Cholangitis

➤ Risks

- Patient
 - Jaundice
- Pancreatic duct
 - Stent for malignant strictures
 - Combined percutaneous cholangiogram (PCC) plus ERCP
 - Inexperienced ERCPist
- Indication
 - Primary sclerosing cholangitis (PSC)
 - Post-liver transplantation, with biliary intervention
- Biliary drainage
 - Failed procedure
 - Klatskin (bifurcation tumour)
 - Avoid filling all intrahepatic ducts
 - Drain contract from ducts at end of procedure
 - Consider placing unilateral stent
 - Avoid iodine contrast (use air)

➤ Prophylactic

- Antibiotics
 - Anticipated / actual obstruction of biliary duct
 - Possible incomplete drainage of ducts

❖ Post-ERCP Stent Complications

- Overall (PD, BD)
 - Obstruction
 - Migration
 - Duct (PD, BD) damage
 - Perforation
 - Abscess
 - Compression of adjacent organ
 - Acute cholangitis
- Pancreatic duct (PD) stent complications
 - PD
 - Irregular ~ 40%
 - Stricture ~ 20%
 - Side branches
 - Dilation ~ 15%



INFLAMMATORY PANCREATIC FLUID COLLECTIONS: ASGE GUIDELINE

Abbreviation: ASGE, American Society for Gastrointestinal Endoscopy

Muthusany VR, et al. Gastrointestinal Endoscopy 2016; 83: 481-488.

➤ Demography

Acute pancreatitis → 20% develop necrosis, of which → 30% develop infection

➤ Types

	Onset, wk
○ Interstitial edematous pancreatitis associated	
- Peri-pancreatic fluid collection (PFC)	< 4
- Pancreatic pseudocyst	> 4
○ Necrotizing pancreatitis associated	
- Acute necrotic collection (ANC)	< 4
- Walled-off necrosis (WON)	> 4

➤ Diagnostic imaging

	Peri-PFC	PPC	ANC	WON
❖ Contrast-enhanced CT scan*				
○ Fluid-density	Homo'	Homo'	Hetero'	Hetero'
- Non-liquid (debris)	-	-	+	+
○ Encapsulating wall	-	+	-	+
○ Location	Out	Out (usually)	In / out	In / out

Abbreviations: ANC, acute necrotic collection; Hetero', heterogenous appearance of fluid; Homo', homogenous appearance of the fluid; In, inside the pancreas (parenchymal); Out, outside the pancreas (extrapancreatic); PFC, pancreatic fluid collection; PPC, pancreatic pseudocyst; WON, walled off necrosis

- Give the advantages of MRI / MRCP in the patient with acute pancreatitis.
 - Detects debris
 - Detects rupture of MPD
 - Predicts severity and prognosis
- Give the differential of pancreatic fluid collections (PFC) on diagnostic imaging.
 - Cyst
 - Duplication
 - Neoplasm
 - Pseudoaneurysm



- Peri-PFC
 - Early, resolve spontaneously
 - May progress to form pancreatic pseudocysts
- Pancreatic pseudocysts (PPC)
 - Drain by transmural stenting with nasocystic tube
 - Successful drainage in > 80%, complications in < 16%, recurrence in 18%

SO YOU WANT TO BE A GASTROENTEROLOGIST!

“Pancreatic” pseudocysts are fluid collections arising from the pancreas and peripancreatic tissues that typically result from acute pancreatitis and persist for more than 4 weeks.

- Within this concept, give the meaning of the “disconnected duct syndrome”.
 - Necrotizing pancreatitis in the head and body of the pancreas leaves parenchymal tissue in the tail.
- ANCs
 - Single / multiple
 - Liquid / solid debris
 - Associated with rupture of MPD
 - May be sterile or infected
- WON
 - Single / multiple
 - May be sterile or infected
 - Infection of necrosis usually occurs 2-4 wk after the onset of acute pancreatitis
- Give three clues that the liquid and necrotic debris in the ANC / WON has become infected.
 - Sepsis
 - Clinical deterioration
 - Gas bubbles in lesion on CT / MRI

Drainage	
ANC --> WON / PPC	
No	Yes

➤ Treatment

Surgical procedures for drainage (cyst gastrostomy) or removal of necrotic debris (necrosectomy) are increasingly being replaced by endoscopic drainage

- Endoscopic drainage
 - Indications
 - Symptoms
 - Enlargement > 6 cm (usually symptomatic)
 - Drainage of infection
 - Safety
 - Lower mortality rate (15%) when performed > 4 wk after hospital discharge, as compared with earlier (> 50%)
 - Stop anticoagulants and antiplatelet indications as per guidelines
 - Prophylactic antibiotics (especially for WON)



- Drainage
 - Transmural, with stents
 - 2 double-pigtailed plastic stents +/- nasocystic drainage
 - Self-expandable metal stent (SEMS)
 - EUS-guided cyst puncture and drainage
 - Best for WON to remove both liquid and solid debris
 - Performance
 - Success ~80%
 - 4 interventions per patient
 - Adverse events 36%
 - Mortality rate 6%
 - ↓ SIR / MOF
 - ↓ fistulae
 - Transpapillary
 - A combination of both
 - Multiple drainage sessions may be necessary to drain debris
 - Multiple transluminal gateway technique (MTGT)
 - MTGT versus single tract drainage
 - ↑ clinical success 92% vs 52%
- Follow-up CT scan in 4-6 wk
 - Dilate any obstruction of pancreatic duct, where possible
 - Usual to remove internal stents, but may be left in place especially for
 - Disruption of pancreatic ducts
 - Disconnected duct syndrome
- Recommendations
 - Endoscopic drainage of PFCs to be performed only after sufficient exclusion of alternative diagnoses, such as cystic pancreatic neoplasms and pseudoaneurysms
 - For maturation of the cyst wall of PFCs before endoscopic intervention
 - Symptomatic pancreatic pseudocysts
 - Rapidly enlarging pancreatic pseudocysts
 - All infected PFCs in patients who fail to improve with conservative management alone
 - Drainage of symptomatic sterile necrosis lasting more than 8 weeks after the onset of acute pancreatitis
 - Routine FNA of PFCs is not required to diagnose infected necrosis
 - Endoscopic drainage for initial therapy before surgical drainage of pancreatic pseudocysts
 - EUS for transmural drainage of PFCs in the absence of a luminal bulge or when portal hypertension is suspected
 - Initial endoscopic and/or percutaneous drainage of WON before consideration of endoscopic transmural necrosectomy or surgical and interventional radiology support
 - Using CO₂ when performing transmural drainage procedures



CYSTIC LESIONS OF THE PANCREAS: ASGE / AGA GUIDELINES

Abbreviation: AGA, American Gastroenterology Association; ASGE, American Society for Gastrointestinal Endoscopy

Muthusamy VR, et al. Gastrointestinal Endoscopy 2016; 84: 1-9; and Vege S, et al. Gastroenterology 2015; 148: 819-822.

- Demography
 - 10% of previous age ≥ 70 yr
- Types
 - Intraductal papillary mucinous neoplasm (IPMN) 38%
 - Mucinous cystic neoplasms 23%
 - Serous cystic neoplasms (SCN) 16%
 - Cystic neuroendocrine neoplasms (C-NET) 7%
 - Pseudocyst
 - Others
 - Solid pseudopapillary neoplasm
 - Ductal adenocarcinoma with cystic degeneration

- Note – Pseudocysts and SCN have no malignant potential

	Pseudocyst	IPMN	Mucinous Cystic Neoplasm	Serous Cystic Neoplasm	Cystic Endocrine Neoplasm	Solid Pseudo-Papillary Neoplasm	Ductal Adeno-Carcinoma with Cystic De-generation
Clinical features	History of moderate to severe pancreatitis	History of pancreatitis, abdominal pain, or found incidentally	Usually found incidentally but can cause abdominal pain and a palpable mass if large	Usually found incidentally but can cause abdominal pain and a palpable mass if large	May have clinical features of solid pancreatic endocrine neoplasm	Usually found incidentally; rarely causes abdominal discomfort	Presents with painless jaundice, abdominal / back pain or rarely pancreatitis
Morphology / EUS findings	Anechoic, thick-walled, rare septations, regional inflammatory nodes may be seen	Dilated main pancreatic duct or side branches; may appear as a septated cyst; may have a solid component	Macroscopic, occasionally septated; peripheral calcifications, solid components and regional adenopathy when malignant	Microcystic with a 'honeycomb' appearance; rarely has a macrocystic component; central calcification	Unilocular cyst occupies most of neoplasm	Solid and cystic components	Primarily solid mass with cystic spaces
Fluid characteristics	Thin, muddy-brown	Viscous or stringy, clear	Viscous or stringy, clear	Thin, clear to sero-sanguineous	Thin, clear	Bloody + necrotic debris	Bloody ± debris



	Pseudocyst	IPMN	Mucinous Cystic Neoplasm	Serous Cystic Neoplasm	Cystic Endocrine Neoplasm	Solid Pseudo-Papillary Neoplasm	Ductal Adeno-Carcinoma with Cystic De-generation
Fluid chemistries	Elevated amylase, low CEA	Elevated amylase and CEA	Elevated CEA, low amylase	Low CEA and amylase	Variable	Variable	Variable
Cytology	Neutrophils, macrophage, histiocytes; negative staining for mucin	Mucinous columnar cells with variable atypia; fluid stains positive for mucin	Mucinous columnar cells with variable atypia; fluid stains positive for mucin	Cuboidal epithelium that stains positive for glycogen	Mono-morphic endocrine tumor cells; stains positive for chroma-granin and synapto-physin	Monomorphic cells with round nuclei and eosinophilic or foamy cytoplasm; stains positive for vimentin and a-1-antitrypsin	Malignant adenocarcinoma may be seen, but varying degrees of atypia may be present in the specimen
Malignant potential	None	Yes	Yes	Almost none (rare reports)	Yes	Yes	Already present

Abbreviations: IPMN, Intraductal papillary mucinous neoplasm; CEA, carcinoembryonic antigen

➤ Diagnostic methods

❖ Endoscopic ultrasound (EUS)

- Even cysts ≤ 2 cm may be malignant (20%), or have malignant potential (45%)
- Multiple small (< 3 mm) cysts within a larger cystic lesion (microcystic lesion) is $> 90\%$ accurate for the pancreatic cysts being serous / benign
- EUS is not reliable to determine if IPMN is benign or malignant
 - Features which $\uparrow$ risk of IPMN being malignant
 - Cysts
 - Size > 3 cm
 - Solid component
 - MPN
 - $\uparrow$ diameter (dilated) ≥ 10 mm
 - Protruding polyps ≥ 4 cm
 - Distinguish mucus from epithelial nodules $\rightarrow$ features of mucus are:
 - Well defined
 - Hypoechoic centre
 - Hyperechoic rim

❖ Fine Needle Aspiration (FNA)

- Analysis for cytology, amylase / lipase / CEA, molecular studies
- Best use of EUS-FNA
 - Cyst > 3 cm
 - Any nodule / mass
 - $\uparrow$ MPD
- Give prophylactic antibiotics for 3-5 d after EUS-FNA for pancreatic cystic lesions



❖ Cytology

- Sensitivity ~60%
- Specificity ~90%
 - Pseudocyst ■ WBC, neutrophils, macrophages, histiocytes
 - Serous ■ Glycogen-rich fluid

❖ Biochemistry, Tumour Markers

- Amylase < 250 U/L
 - Excludes (98% specific) a pseudocyst
- CEA
 - Performance characteristics depend upon cut-off concentration
 - None of the tumour markers are "... accurate enough to provide a definitive diagnosis"

❖ ERCP / Pancreatography

○ ERCP – Not usually used for cystic lesions – Biopsy by ERCP low diagnostic lesion ○ Pancreatography ○ Mucus flowing from wide pancreatic orifice – Pathognomonic for malignant lesion – Only seen in 20 - 55% of MPD IPMNs	○ Narrow pancreatic duct differential – Malignancy – Pancreatitis, chronic – Trauma ○ Dilated MPD / blunted side branches – Chronic pancreatitis – IPMN ○ Communication of cyst with MPN – Pseudocyst – IPMN
- Pancreatography may be combined with intraductal ultrasound

Abbreviations: MPD, main pancreatic duct

➤ Recommendations

- EUS-FNA of any (on cross-sectional or EUS) pancreatic cystic lesion > 3 cm in diameter image confirms
 - Epithelial nodule
 - Dilated main pancreatic duct or
 - Suspicious mass lesion
- EUS-FNA is optional in asymptomatic patients in whom cross-sectional imaging demonstrates a cyst < 3 cm and without either a mass and / or epithelial nodule or associated dilated main pancreatic duct.
- Testing of aspirated pancreatic cystic fluid for CEA, amylase and cytology
- Molecular testing of the cyst
 - Initial ancillary testing of the cyst is inconclusive
 - Test results may alter management
- Prophylactic antibiotics for patients undergoing EUS-FNA for the evaluation of cystic pancreatic neoplasms
- ERCP, pancreatoscopy, and intraductal US may be helpful in the diagnosis and characterization of suspected main duct IPMNs

❖ Surgery

- Resection



LIVER



THE DISEASES

ALCOHOLIC LIVER DISEASE (ALD): AASLD / ACG AND EASL GUIDELINES

Abbreviations: AASLD, American Association for the Study of Liver Disease; ACG, American College of Gastroenterology; EASL, European Association for the Study of the Liver

AASLD. O'Shea RS, et al. Hepatology 2010; 51: 307-328; ACG. O'Shea RS, et al. Am J Gastroenterol 2010; 105: 14-32; EASL. J. Hepatology 2012; 57: 399-420; Singh S, et al. Gastroenterology 2015; 149: 958-970.

➤ Terms

- Alcohol abuse / problem drinkers
 - Negative social and health consequences of alcohol consumption
- Alcohol dependence
 - Physical tolerance and withdrawal from alcohol

➤ Demography

- Risk behaviour
 - > 60 g alcohol / d 90% develop fatty liver
 - > 40 g/d 30% develop cirrhosis
 - > 40-80 g/d for 25 yr 40-60% develop perivenular fibrosis
 - Alcoholic hepatitis 50% develop cirrhosis
 - Alcohol abuse
 - Alcohol dependence
- } Each represent ~4% of adult Americans

➤ Pathophysiology

❖ Fatty Liver

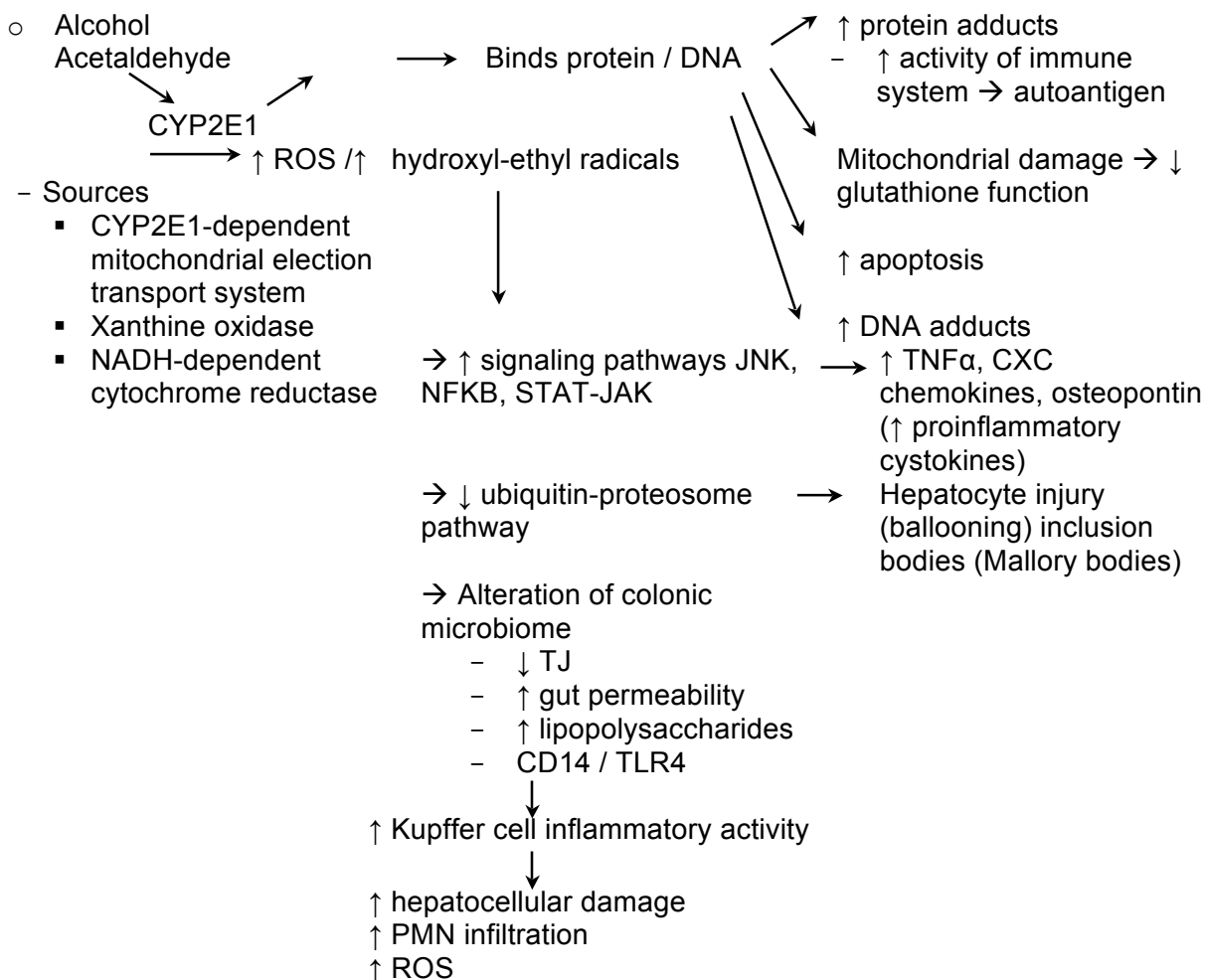
- Alcohol
 - ↑ acetaldehyde → ↓ NADH oxidation – Mitochondrial damage
 - ↑ VLDL accumulation
 - ↑ NADH → ↑ synthesis of FA, TG
 - ↓ B-oxidation of FA by hepatocyte mitochondria
 - ↓ PPARA / ↑ SREBP 1c → ↓ AMPK → ↑ lipogenesis
 - ↓ lipolysis
- Sources of FA
 - Intestine
 - Adipose tissue

} ↑ synthesis of FA, TG

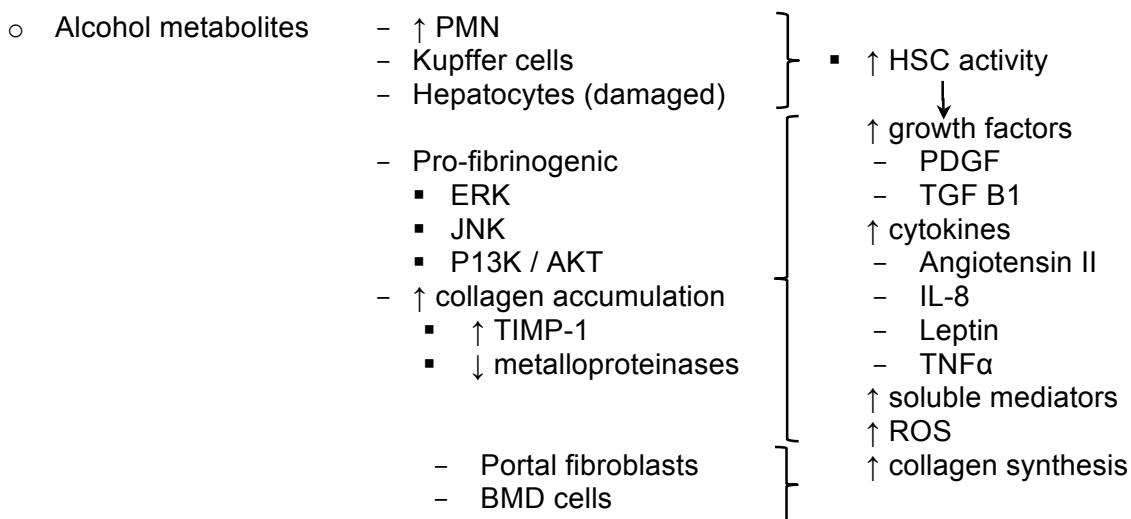
Abbreviations: AMPK, adenosine monophosphate activated kinase; FA, fatty acids; PPARA, peroxisome proliferating-activated receptor alpha; SREBP 1c, steroid regulatory element binding protein 1c; TG, triglyceride; VLDL, very low density lipoprotein



❖ Steatohepatitis



❖ Fibrosis



Abbreviations: BMD, bone marrow derived cells; HSC, hepatic stellate cells; ROS, reactive oxygen species; TJ, tight junctions



➤ Risk factors

- Alcohol
 - Total alcohol burden (g alcohol/d x duration of exposure > 30 g/d, lifetime alcohol intake > 100 kg)
 - Risk is only partially related to dose of alcohol consumed
 - Timing
 - Alcohol not consumed with meals
 - ↑ risk 2.7x
 - Binge drinking

M > 5
F > 4

}

Drinks per sitting
- Patient
 - Gender
 - “Safe” limit of alcohol intake (units per wk)

M 21 (168 g alcohol)
F 19 (112 g alcohol)
 - Race
 - Risk of cirrhosis
 - African American M / F
 - Hispanic M
 - Risk of death from cirrhosis
 - Hispanic M
 - Comorbidities
 - HCV infection
- Diet
 - Malnutrition
 - Protein-calorie deficiency
 - Micronutrients: ↓ vitamin A / E
 - Obesity
 - ↑ body weight
- Genetic factors
 - Gene polymorphous induced in metabolism of alcohol
 - Alcohol dehydrogenase
 - Acetaldehyde dehydrogenase
 - Cytochrome P450
 - Genes related to regulation of endotoxin-mediated release of cytokines

➤ Clinical

- Routinely screen for alcohol abuse, using validated questionnaires
 - CAGE ≥ 2 out of 4 questions positive
 - Sensitivity ~70%
 - Specificity 90%
 - AUDIT

▪ Sensitivity 51-97%
▪ Specificity 78-96%

}

Identifies persons at risk for dependence or abuse



Alcohol abuse (aka harmful alcohol use, or “risky drinker”) can be screened by asking patients AUDIT question #3 “How often do you have six or more drinks in one occasion?”

- Also screen for psychiatric comorbidity e.g., anxiety, depression, schizophrenia
 - Screen for other addictive behaviour, including
 - Tobacco (smoking)
 - Food (obesity)
 - Illicit drugs
 - Findings related to alcohol abuse
 - CNS / PNS
 - Neurotoxicity
 - Alcoholic dementia
 - Peripheral neuropathy
 - Delirium tremors
 - Coma
 - Seizures
 - Heart
 - Cardiomyopathy
 - Cardiac arrest
 - MSK
 - Muscle wasting
 - Kidney
 - IgA nephropathy
 - Pancreas
 - Insufficiency
- } Alcohol withdrawal syndrome (AWS)
- Give the features on physical examination which suggest ↑ risk of mortality in 1 yr in the person with alcoholic liver disease.

Findings	Relative Risk
○ Hepatic encephalopathy	4
○ Ascites	4
○ Spider nevi	3.3
○ Peripheral edema	2.9
○ Caput medusa	2.2
○ Fatigue	2.1

Clinical Skills

- Give the features on physical examination in the patient with alcoholism which suggest the presence of cirrhosis.
 - Parotid glands - Enlarged
 - Hands - Dupuytren contracture
 - Feminization - Extensive spider angiomas



➤ Genetics

- Genetic factors may represent ~50% of individuals susceptibility to develop ALD
- There are numerous genes and single nucleotide polymorphisms (SNPs) have been identified
 - Two genes which may be important in the pathogenesis of ALD include
 - PNPVA3
 - rs738409 (GG)

Clinical Pearl and Gem

- Give the chemical significance of finding Mallory hyaline bodies on histological examination of liver biopsy material in the patient with ALD.
 - In the patient with ALD, the histological detection of Mallory bodies suggests recent active drinking of alcohol.
- Give the best histological predictor for the development of fibrosis.
 - About 40% of persons with alcoholic steatohepatitis will progress to the development of fibrosis progressing to cirrhosis.

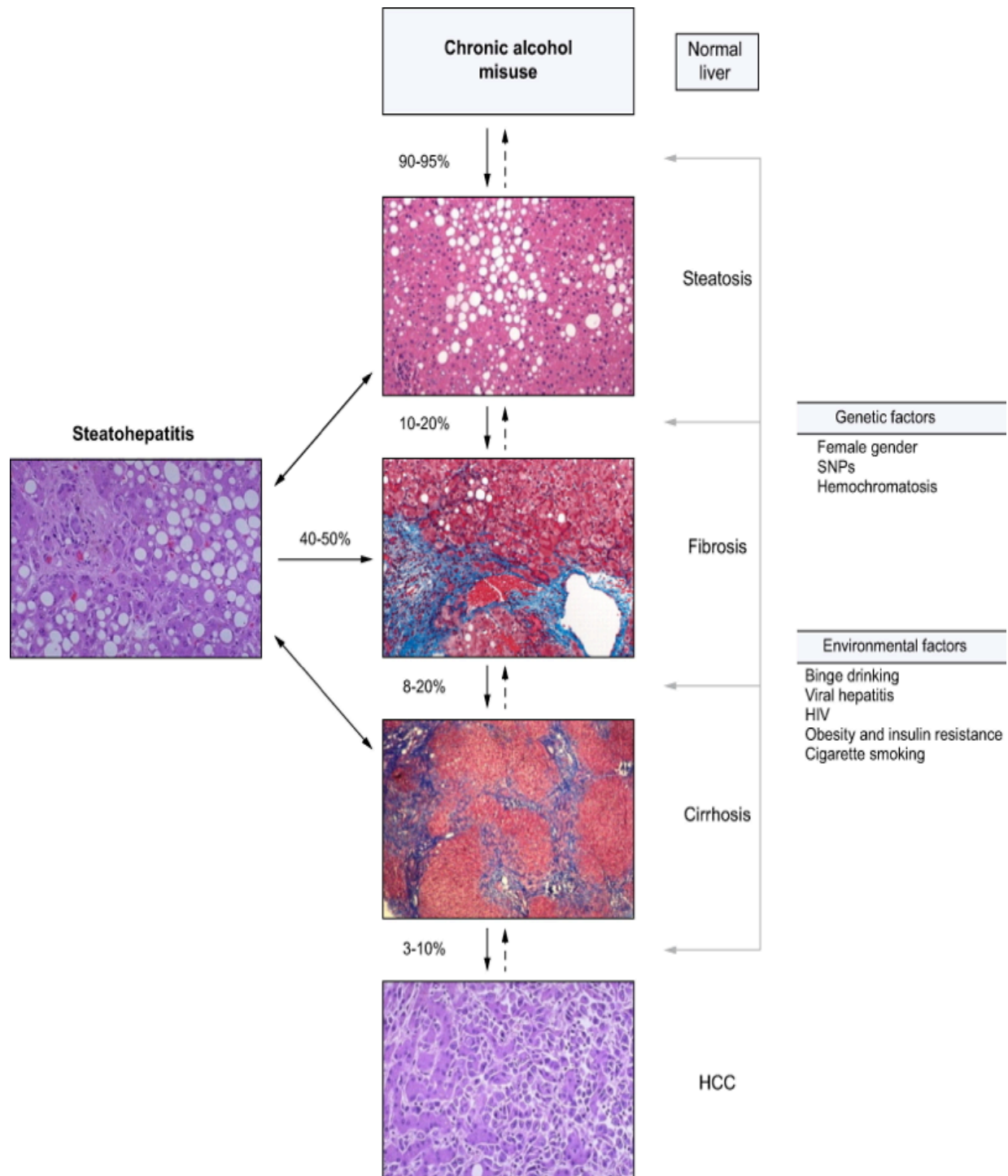
➤ Laboratory

- Biomarkers
 - ↑ AST 2-6x ULN
AST > ALT 2:1
 - Asymmetric dimethylarginine and stereoisomer
- Give the performance characteristics for laboratory markers for daily intake of alcohol > 50 g.

	Sensitivity	Specificity
○ Carbohydrate specific transferrin (CDT)	69%	92%
○ Gamma-glutamyl transferase (GGT)	73%	75%
○ Mean cell volume (MCV)	52%	85%
○ AST	50%	82%
○ ALT	35%	86%
○ Physical examination		



➤ Histopathology



Natural history of alcoholic liver disease (ALD). The spectrum of ALD is comprised of steatosis, steatohepatitis, fibrosis, cirrhosis, and superimposed hepatocellular

Printed with permission: EASL. J Hepatology 2012; 57: 399-420.



- Feature
 - Hepatocyte ballooning
 - Megamitochondria
 - Neutrophilic (polymorphonuclear cell, PMN) infiltration in lobules
 - Mallory bodies
 - Lobular distortion
 - Fibrosis (trichrome or Sirius red staining)
 - Micronodules
 - Cirrhosis
- Prevalence of histological features in heavy drinkers
 - Normal 14%
 - Steatosis 28%
 - Hepatitis 9%
 - Fibrosis +/- steatosis 20%
 - Cirrhosis 29%

Alcoholic Hepatitis

- Give the definition for alcoholic hepatitis (steatohepatitis).
 - Alcoholic hepatitis is a clinical syndrome of continued alcohol use leading to the worsening of underlying alcoholic liver disease, and characterized by recent onset of jaundice +/- ascites, encephalopathy, bleeding esophageal varices, and hepatorenal syndrome.
- Diagnostic imaging
- Give the features seen on diagnostic imaging of the liver which suggest alcohol as the basis for underlying chronic liver disease.
 - Caudate lobe enlarged
 - Right posterior hepatic notch prominent
 - Nodules smaller (regenerative nodules → micronodular cirrhosis)
 - Overall, transient elastography (FibroScan®) is a “reliable tool” for assessing the degree of fibrosis in ALD, but the clinician must take into consideration the possible presence of factors which can result in an overestimation of the amount of fibrosis.
- Give factors which can lead to an over-estimate of the extent of fibrosis (as measured by FibroScan®) in the liver of a patient with ALD.
 - Steatohepatitis (transaminases)
 - Congestion (RBCs)
 - Cholestasis
 - Recent intake of alcohol



➤ Histopathology

- A spectrum of fatty liver, steatohepatitis, fibrosis / cirrhosis
- No changes are pathognomonic for ALD
 - Parenchyma, lobules
 - Inflammation (neutrophil / polymorphonuclear [PMN] cells)
 - Necrosis (Mallory hyaline)
 - Periportal
 - Fibrosis
 - Bile duct proliferation (cholestasis)
 - Perivenular fibrosis and fibronectin
 - Sinusoids
 - Intrasinusoidal and pericentral collagen
 - Hepatocytes
 - Ballooning degeneration
 - Megamitochondria
 - Nuclear vacuolation
- Note: Liver biopsy performed in ALH only if diagnosis is uncertain.

➤ Prognostic factors

- Give the histological features of the liver biopsy in a person with ALD which predict a good versus a bad prognosis.

Prognostic Predictors	
Good	Bad
○ Megamitochondria	– ↑ PMN – ↑ cholestasis

- Give Scoring systems for prognosis of ALD.
 - Maddrey discriminant function (MDF) score
 - = $4.6 (\text{PT of patient} - \text{control}) + \text{total bilirubin (mg/dL)}$
 - MDF score > 32
 - Mortality rate at 1 mon 30 - 50%
 - Higher end of range if there is associated hepatic encephalopathy (HE)
 - Model for End-Stage Liver Disease (MELD) score
 - = $3.6 \times \log_e (\text{bilirubin, mg/dL}) + 11.2 \times \log_e \text{INR} + 9.6 \times \log_e \text{creatinine (mg/dL)} + 6.4$
 - A change in MELD score ≥ 2 points during first week in hospital predicts mortality rate
 - Glasgow Alcoholic Hepatitis (GAH) score, calculated on days 1 and 7 of hospitalization
 - Based on PT ratio, bilirubin, urea, WBC, patient age
 - Higher accuracy than MDF or MELD score
 - Lower sensitivity to predict mortality rate at 1 and 3 mon
 - Child-Turcotte-Pugh (CTP) score



- Note: The performance characteristic of MDF and the MELD score for the prediction of the prognosis of alcoholic hepatitis depend upon the cut-off values chosen.
 - For example, for MDF score ≥ 32 and MELD score > 11 to 18
 - Sensitivities range from 76 - 86%, and 75 - 85% for MELD
 - Specificities range from 48 - 75% for MDF, and 75 - 81% for MELD
- Lille score is used to estimate the prognosis of AH in persons treated with corticosteroids (CS), and as such is useful to determine if CS should be continued or discontinued
 - www.lillemodel.com

Feature	Prognostic Involvement					
	MDF	MELD	GAHS	ABIC	Lille	CTD
○ Bilirubin	+	+	+	+	+	+
○ PT / INR	+	+	+	+	+	+
○ Cr / Urea		+	+	+	+	
○ Patient age			+	+	+	
○ Albumin				+	+	+
○ WBC			+			
○ Δ Bilirubin day 1 to 7					+	
○ Ascites, hepatic encephalopathy						+

Abbreviations: ABIC, age bilirubin INR creatinine; CTP, Child-Turcotte-Pugh; GAHS, Glasgow alcoholic hepatitis score; MDF, Maddrey discriminant function; MELD, Model for end-stage liver disease

Adapted from: EASL Clinical Practice Guidelines. J Hepatology 2012; 57: page 410, table 3.

SO YOU WANT TO BE A HEPATOLOGIST!

Fatty liver from alcohol intake and from obesity/metabolic syndrome (non-alcoholic fatty liver disease) have several similar steps in the pathophysiology of hepatic steatosis.

- Give components of the causation of NAFLD (steatohepatitis, fibrosis/cirrhosis) which would accelerate ALD.
 - $\uparrow$ BMI $\rightarrow$
 - $\uparrow$ angiotensin II
 - $\uparrow$ leptin
 - $\downarrow$ adiponectin

➤ Aide de memoire

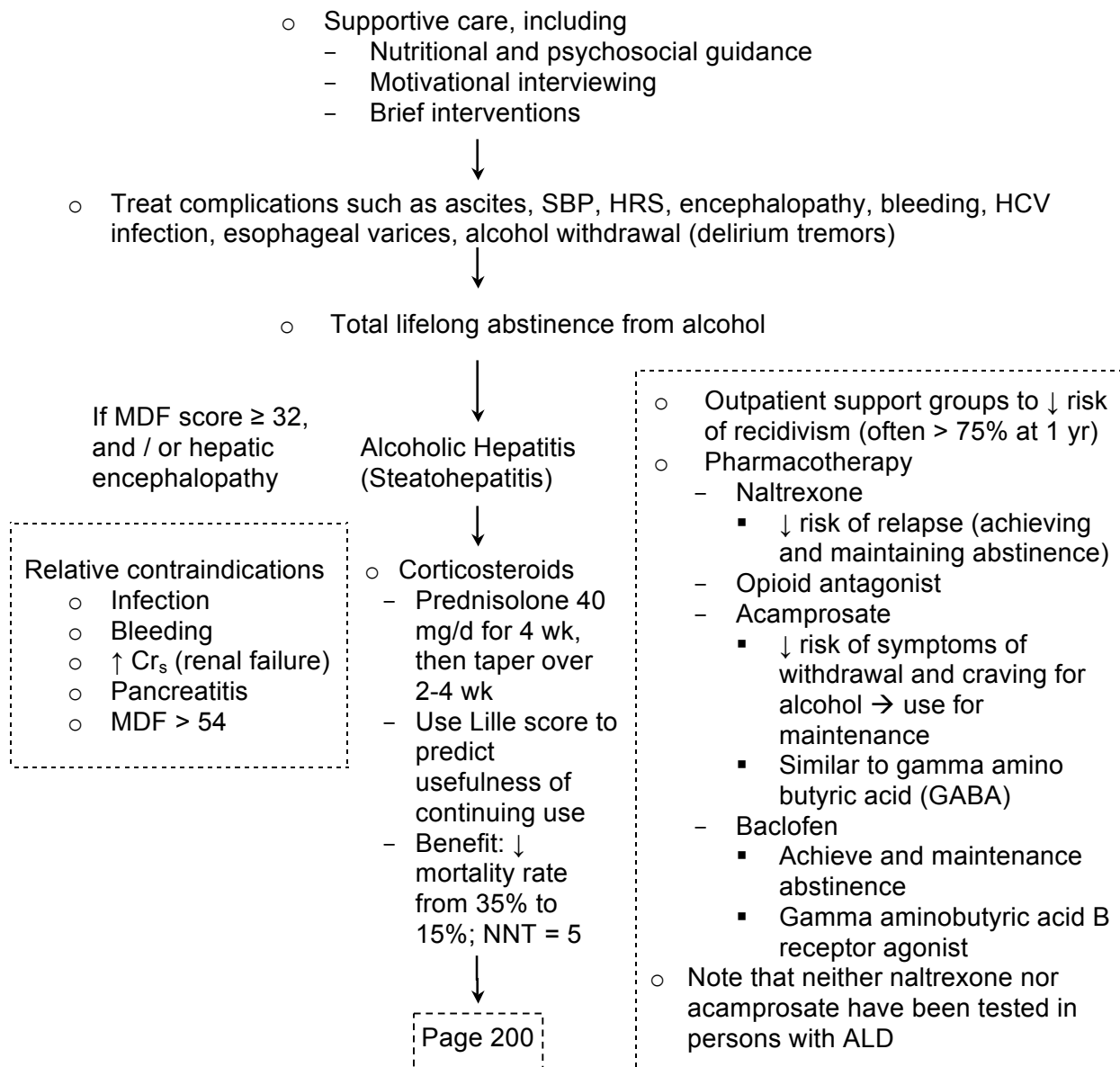
- CTP

As, HE, Alb, bilirubin $\longrightarrow$ MDF $\xrightarrow{+Cr_s}$ MELD $\xrightarrow{+age}$ Lille

Abbreviations: bili, bilirubin concentration; Cr_s, serum creatinine; CTP, Child-Turcotte-Pugh; INR, international normalized ratio; MDF, Maddrey discriminant function; MELD, Model for end stage liver disease



➤ Treatment



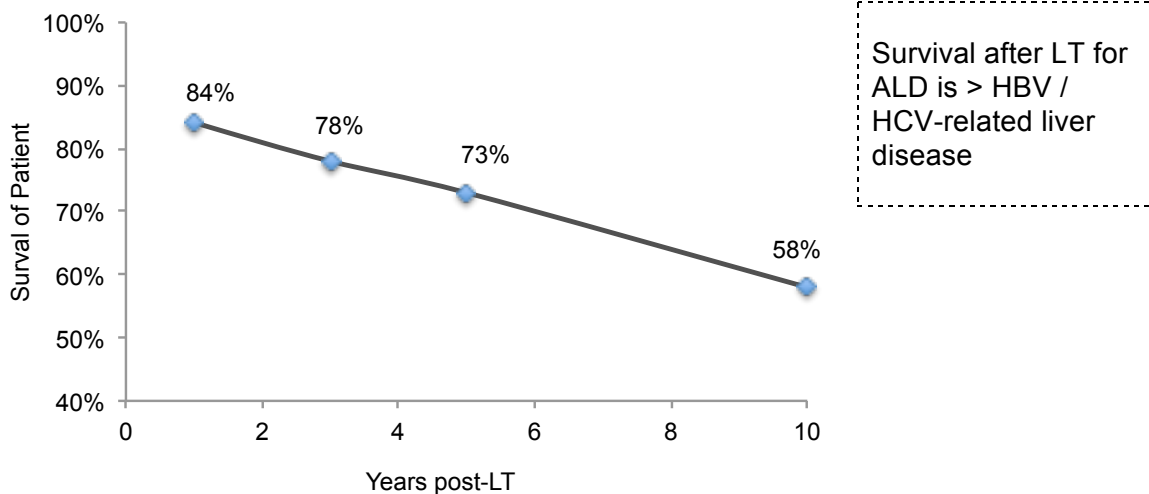
Need more data (NMD)

- Alcohol depletes glutathione stored in hepatocytes.
- N-acetylcysteine (NAC) replenishes hepatocyte stores of glutathione, and also has an anti-oxidant effect.
- Administering NAC plus corticosteroids in persons with alcoholic steatohepatitis increases but not 6-mon rates of hepatorenal syndrome
- Infection and death

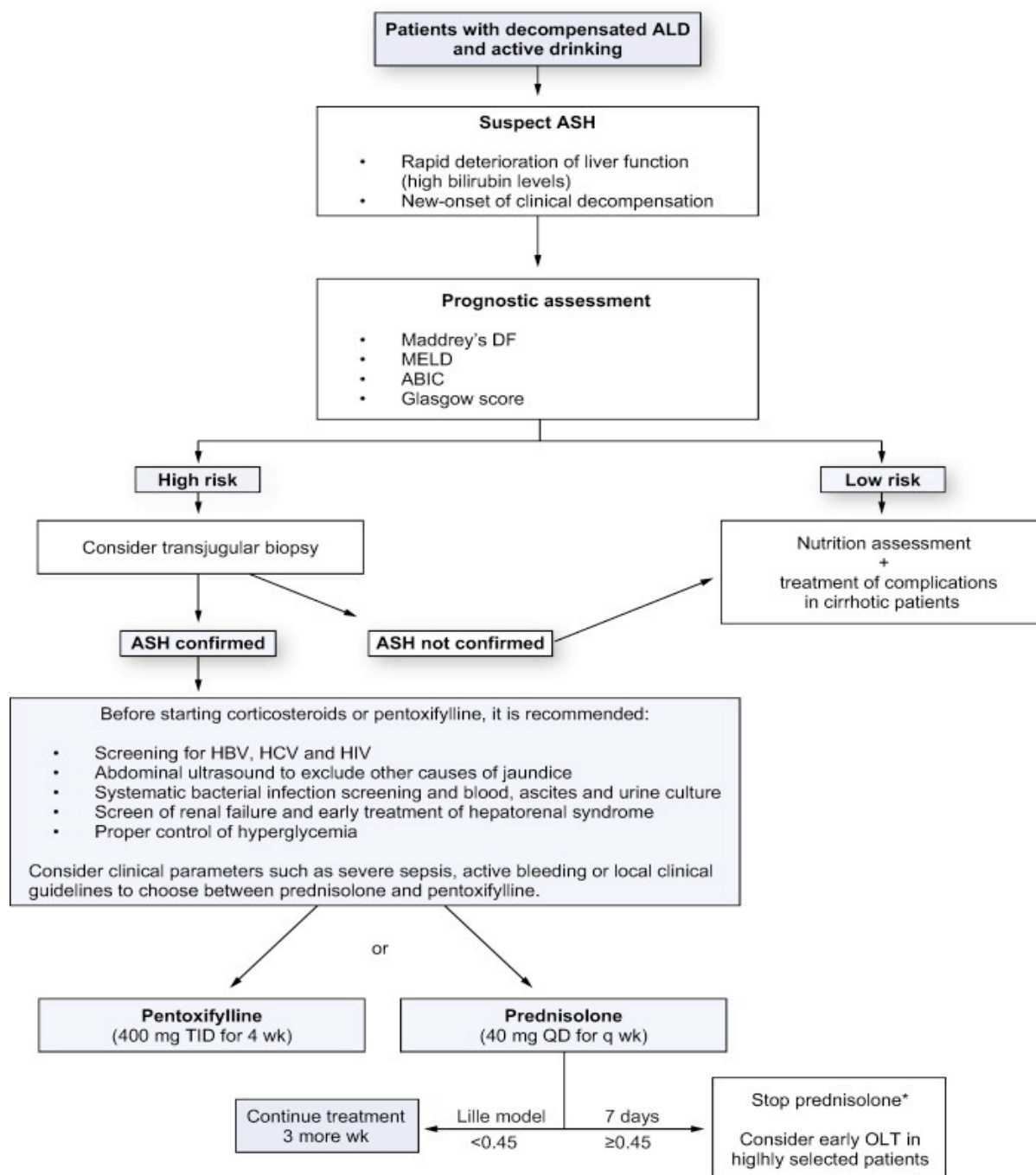


- ↓
- Pentoxifyline 400 mg po tid x 4 wk
 - Phosphodiesterase inhibitor
 - Use when
 - Corticosteroids contraindicated
 - ↑ Cr_s (serum creatinine)
 - ↓ risk of hepatorenal syndrome (HRS)
 - Debatable benefit on mortality
- ↙ ↘
- Long-term care
 - Manage complications
 - HCC surveillance q 6 mon
 - Regular medication review
 - Monitor for minimal (occult) hepatic encephalopathy
 - Screen for anxiety, depression, suicide ideation
 - Smoking cessation
 - Exercise program
 - Screening for ↑ risk of coronary heart disease / peripheral vascular disease
 - Age-appropriate screening
 - Updating vaccinations

- Liver transplantation
 - Trial of total abstinence
 - Risk of recidivism ("relapse", any intake of alcohol) at 3-5 yr after liver transplantation for ALD, 11 - 49%
 - Most of these persons who resume intake of alcohol do not become heavy / abusive users



➤ Therapeutic algorithm for the treatment of patients with alcoholic steatohepatitis (ASH)



*A Lille score ≥ 0.45 indicating non-response and increased risks of infection and death. In non-responders, the interruption of corticosteroids is recommended particularly in those classified as null responders (Lille score >0.56).

Printed with permission: EASL. J Hepatology 2012; 57: 399-420.

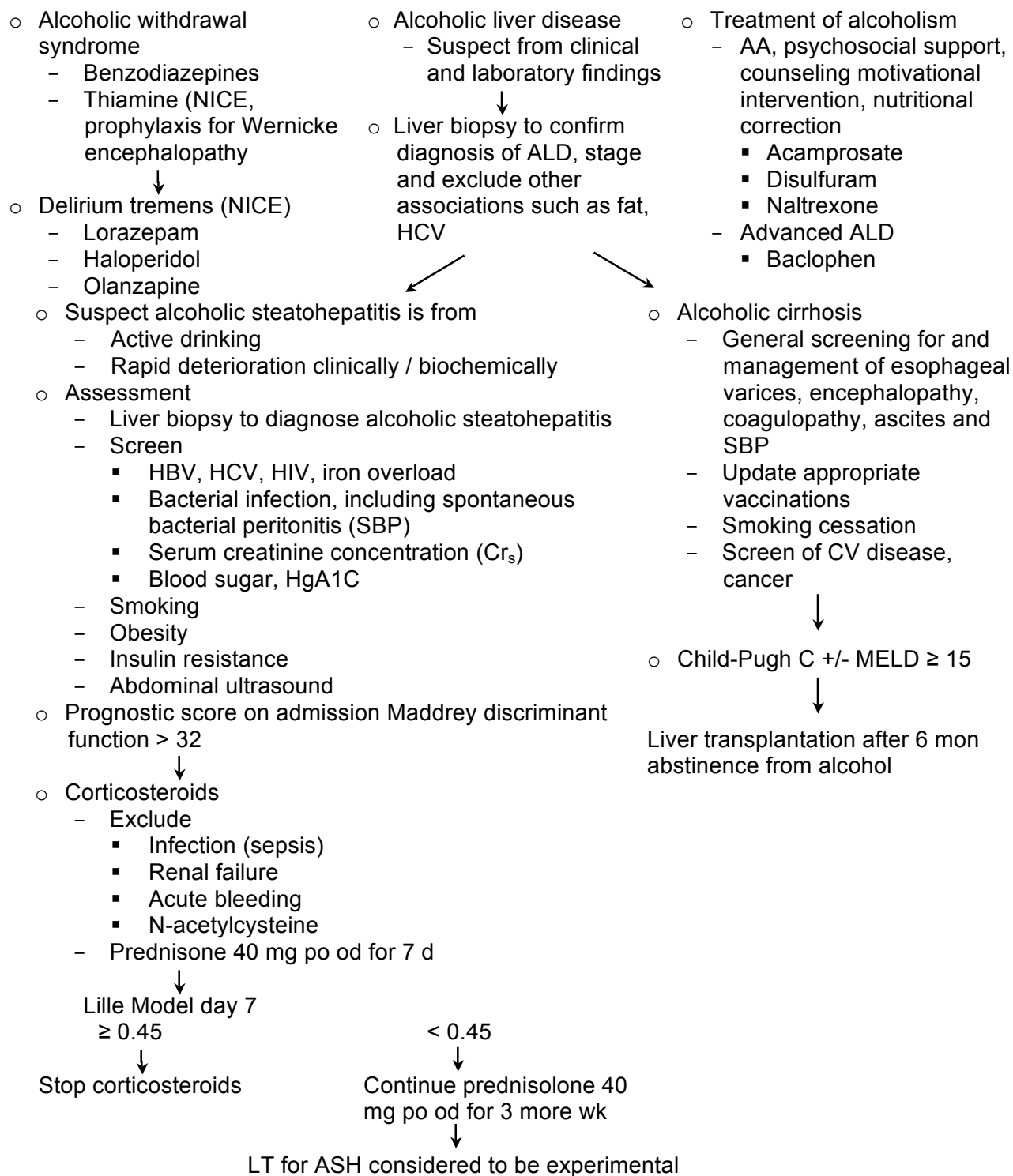


Alcoholic Liver Disease (ALD): EASL / NICE Guidelines

Abbreviations: EASL, European Association for the Study of the Liver; NICE, National Institute for Health and Care Excellence

EASL. J Hepatology 2012; 57: 399-420; and www.nice.org.uk/cg100.

Regular Primary Care Audit Questionnaire for screening for ALD



NON-ALCOHOLIC FATTY LIVER DISEASE (NAFLD)

Non-Alcoholic Fatty Liver Disease (NAFLD): AASLD / EASD / EASL / EASO / NICE Guidelines

Abbreviations: AASLD, American Association for the Study of Liver Disease; EASD, European Association for the Study of Diabetes; EASL, European Association for the Study of the Liver; EASO, European Association for the Study of Obesity; NICE, National Institution for Health Care Excellence

AASLD: Chalasani N, et al. Hepatology 2012; 55: 2005-2023; EASL-EASD-EASO Clinical Practice Guidelines. J Hepatology 2016; 64(6): 1388–1402; Ahmed A, et al. Clin Gastroenterol Hepatol 2015; 13: 2062-2070.

Please see NICE guidelines 2016 (www.nice.org.uk/guidance/ng49)

➤ Definition

- ↑ triglyceride in the liver in persons who do not use excessive alcohol and in whom there are no concurrent disorders associated with fatty liver.
 - ↑ liver fat
 - Histological analysis > 5%
 - Proton density fat fraction (proton MR spectroscopy) > 5.6%
 - ↑ alcohol intake per day
 - Men ≥ 30 gm
 - Women ≥ 20 gm
 - There are surrogate markers for NAFLD, but the definitive diagnosis of non-alcoholic steatohepatitis requires a liver biopsy showing steatosis, hepatocyte ballooning and lobular necroinflammation.

➤ Demography

- 1/3 of population, including both those of ↓ as well as ↓ BMI
- Risk factors for the progression of NAFLD → NASH
 - > 50 yr
 - Type II diabetes mellitus (T2DM)
 - Metabolic syndrome (MetS)
 - Waist circumference
 - M ≥ 94 cm
 - F ≥ 80 cm
 - Blood pressure
 - ≥ 130 / 85 mm Hg or
 - Treatment for hypertension
 - Glucose, fasting
 - ≥ 5.6 mmol/L, ≥ 100 mg/dL, or treatment for T2DM
 - Triglyceride > 1.7 mmol/L, 150 mg/dL
 - HDL cholesterol
 - M < 1.0 mmol/L
 - F < 1.3 mmol/L



- Prevalence varies depending upon measurement tool, e.g., aminotransferase (ALT, AST), abdominal ultrasound, or liver histology
 - Estimated worldwide prevalence (median)
 - NAFLD 20%
 - NASH 5%
 - ↑ prevalence varices with age, gender, ethnicity, presence of metabolic syndrome, obesity, DM T2
- Subtypes of NAFLD
 - Non-alcoholic fatty liver (NAFL, aka simple steatosis)
 - Non-alcoholic steatohepatitis (NASH)
 - Hepatic steatosis
 - Inflammation
 - Hepatocyte ballooning
- Causes / associations (independent of obesity)
 - Endocrine
 - Pituitary ▪ Hypopituitarism
 - Thyroid ▪ Hypothyroidism
 - Liver ▪ Dyslipidemia
 - Wilson disease
 - HCV infection
 - PBC
 - Pancreas ▪ Type II diabetes mellitus
 - Pancreato-duodenal resection
 - Gonads ▪ Hypogonadism
 - Polycystic ovary syndrome
 - Sleep apnea
 - Malnutrition
 - Parenteral nutrition
- Give the conditions other than diabetes or metabolic syndrome which need to be excluded before making the diagnosis of primary NAFLD.
- ❖ Hepatic
 - Inherited - Lysosomal acid lipase deficiency
 - Infection - HCV infection, genotype 3
 - Infiltration - Hereditary hemochromatosis
 - Wilson disease
 - Immune - Autoimmune hepatitis (AIH)
 - Toxins - Alcohol, drugs

Curiosity

- Primary biliary cholangitis (PBC) is associated with steatosis (~40%) and steatohepatitis (15%)



❖ Non-hepatic

- GI
 - Celiac disease
 - Starvation
 - Parenteral nutrition
- Endocrine
 - Hypopituitarism
 - Hypothyroidism
 - Hypogonadism
 - α -hypebetalipoproteinemia
 - Polycystic ovary syndrome (POS)
- Lung
 - Obstructive sleep apnea

SO YOU WANT TO BE A GASTROENTEROLOGIST!

- Give the name of the gastric modifiers of NAFLD.
 - PNPLA3
 - PNPLA3 rs 738409 variant
 - TMGF2

➤ Mortality rate

- NAFL, NASH cardiovascular disease
- NASH liver related causes e.g., HCC with advanced fibrosis or cirrhosis

➤ Laboratory (epiphenomenons)

- $\uparrow$ transferrin saturation, $\uparrow$ ferritin
 - $\uparrow$ autoantibodies
 - ANA > 1: 160
 - ASMA > 1: 40
- } In 20% of NAFLD patients

Abbreviations: ANA, anti-nuclear antibody; ASMA, anti-smooth muscle antibody

- Give the performance characteristics of laboratory measures to predict the presence of histologically confirmed advance fibrosis (bridging fibrosis / cirrhosis) in NAFLD.

Measure	Sensitivity	Specificity	AUROC
○ NAFLD fibrosis score			0.85
< - 1.455	90%	60%	
> 0.676	67%	97%	
○ Enhanced liver fibrosis (ELF)	80%	90%	0.90
○ Cytokeratin-18 (CK 18)			



- Variables
 - NAFLD fibrosis score

Formula
<http://nafld-core.com>

- ELF panel

- Age
- BMI
- AST / ALT ratio
- Platelet concentration
- Blood glucose
- Hyaluronic acid
- P III NP
- TIMP-1

Abbreviations: AUROC, area under the receiver operator curve; BMI, body mass index; ELF, enhanced liver fibrosis

➤ Laboratory (steatosis score)

- Fatty liver index (FLI)
- SteatoTest®
- NAFLD liver fatty score (LFS)

} Predict pressure of NAFLD, CVS outcomes and mortality

- NAFLD fibrosis score (NFS)
- Fibrosis 4-calculator)
- Enhanced liver fibrosis (ELF) score
- FibroTest®

} Predict mortality overall, as well as hepatic and CVS-mortality

- HOMA-IR

- A surrogate marker for insulin resistance (IR)
- All components of the metabolic syndrome correlate with hepatic content of fat (independent of BMI)
- $\text{HOMA-IR} = \frac{\text{Fasting blood glucose (FBS, mmol/L)} \times \text{Insulin (mU/mL)}}{22.5}$

22.5

- MRI

- Gold standard for quantitation of hepatic fat (including when distribution is patchy)

- Transient elastography (TE)

- NPV > PPV, so not adequate for all aspects of decision-making in NAFLD
- No reliable with ↑ BMI or ↑ thoracic fold thickness
- Better for F4 than F3

➤ Clinical

- Evaluate for evidence of

- Metabolic syndrome
- Hepatic and non-hepatic associations with NAFLD
- Hepatic conditions not related to NAFLD (e.g., HAV, HBV)
- Presence of signs of
 - Portal hypertension
 - Decompensated cirrhosis
 - EV
 - Ascites, SBP, HRS
 - HE
 - HCC

Abbreviations: EV, esophageal varices; HCC, hepatocellular cancer; HE, hepatic encephalopathy; HRS, hepatorenal syndrome; SBP, spontaneous bacterial peritonitis; T2DM, type 2 diabetes mellitus



Clinical Gem

- Remember that
 - NAFLD is associated with obesity and T2DM and vice versa
 - There are all independently associated with ↑ risk of HCC

➤ Follow-up

	<u>yr to progress 1 fibrosis stage</u>
○ Rational	
- NAFLD	4
- NAFLD plus hypertension	7
- Access ongoing BMI, Mets, T2DM, liver enzymes and function tests, any associated liver disorders, complications of cirrhosis / portal hypertension
 - Cardiovascular disease (CVD)
 - Frequency of follow-up

	<u>Follow up in yr</u>
- NAFLD suspected but not confirmed; ALT / AST normal confirmed	q 3 – 5
- ALT / AST normal	q 2 yr
- Cirrhosis	At least q 1 yr (US for HCC q 6 mon)

➤ Pathology

- “Liver biopsy is essential for the diagnosis of NASH and is the only procedure that reliably differentiates NAFL from NASH” (even though there is sampling variability in liver biopsy changes of fat, hepatocyte ballooning, necroinflammation and fibrosis / cirrhosis).
- Give the subclassification of NASH based upon the fibrosis (F) score.

Adjective	F Score	Fibrosis
Early	0-1	- / mild
Fibrotic	≥ 2	Significant
	≥ 3	Advanced (bridging)
Cirrhosis	F4	

- Give the scoring systems.
 - NAFLD activity score (NAS)-correlated with
 - Correlated with

▪ ALT/AST ▪ HOMA-IR	}
 - Not for diagnosis or to assess prognosis, but
 - For assessing severity
 - Steatosis, activity and fibrosis) score
 - Paediatric histological score (PHS)



➤ Treatment

❖ Lifestyle

- Diet
 - Calories defect of 500 - 1000 kcal/d, healthy diet
 - Fat, low / moderate
 - CHO moderate / high or
 - Low ketogenic or high protein
 - Low alcohol intake
 - No fructose intake
- Habitual aerobic exercise / resistance training

❖ Pharmacology

- Thiazolidinediones (glitazone)
 - Pharmacology
 - Peroxisome proliferator-activated receptor (PPAR γ) agonist
 - Insulin-sensitizing effects, useful to treat T2DM or prediabetes
 - Benefits
 - ↓ NASH histological changes except fibrosis
 - Adverse effects
 - ↑ body weight gain
 - Bone fractures in women
 - ↑ heart failure
- Vitamin E 800 IU/d
 - Antioxidant
 - Non-cirrhotic (biopsy-proven), non-diabetic patients with NASH
 - ↓ NASH pathology (ballooning, inflammation, steatosis)
 - Adverse effects
 - ↑ stroke, hemorrhagic
 - ↑ prostate cancer, men > 50 yr
 - May ↑ overall mortality

❖ Surgery

- Bariatric surgery
 - ↓ metabolic syndrome
 - ↓ BMI
 - ↓ histological changes of NASH
 - Clearing of NASH 88%
 - ↓ fibrosis ~35%
- Liver transplantation (LT)
 - With more efficient treatment for HCV infection, LT for NASH is becoming much more common
 - Survival of patient out to 5 yr as in non-NAFLD patient
 - Transplant (graft) failure low
 - NASH cirrhosis
 - Rarely recurs
 - ↑ risk of cardiovascular disease and sepsis post LT



Non-alcoholic Fatty Liver Disease (NAFLD): AASLD Guidelines

Abbreviations: AASLD, American Association for the Study of Liver Disease

Chalasani N, et al. Hepatology 2012; 55: 2005-2023.

➤ Diagnosis (NAFLD)

- Hepatic steatosis (histology or diagnostic imaging) less than “significant” intake of alcohol intake, no competing etiologies for hepatic steatosis and no other (co-existing) cause for chronic liver disease.
- Suspected from
 - Transaminitis (↑ ALT, ↑ AST
 - Abdominal ultrasound
 - Presence of obesity, metabolic syndrome
 - Presence of other types of liver disease (e.g., HCV, PBC)
 - No significant alcohol intake (drinks per week < 21 for M, < 14 for F)
- Risk stratification
 - Metabolic syndrome, plus
 - ↑ NAFLD Fibrosis Score

↓
- Consider liver biopsy
 - Possible other liver disease
 - Co-existing, or
 - Associated with steatosis

↓

➤ Treatment

- Hypocaloric diet plus
 - Exercise program
 - Target ↓ body weight of ~5% (↓ liver fat ~30%)
 - Suggest reduction of non-significant alcohol consumption (author’s suggestion, not an AASUA suggestion)
- Pharmacological measures

– Pioglitazone 45 mg/d	▪ Biopsy-proven NASH ▪ ↑ risk (0.5%) of heart failure ▪ Monitor for ↑ risk of heart failure ▪ Monitor for ↑ BMI
– Vitamin E 800 U/d	▪ Biopsy-proven NASH, plus ▪ Non-diabetic ▪ ↓ AST / ALT ▪ ↓ steatosis, inflammation, ballooning, but not fibrosis ▪ ↑ risk of all-cause mortality, plus ↑ risk of prostate cancer (↑ absolute risk of 160 / 10⁵) ▪ No personal or family history of prostatic cancer (author’s suggestion, not an AASUA recommendation)



- For NAFLD-associated conditions



- Metformin
 - Use if there is associated prediabetes
 - 6-12 mon of lifestyle changes plus metformin does not improve AST / ALT or hepatic histology
- Statins
- Omega-3 fatty acids for associated hypertriglyceride



- Screening / surveillance for NASH-associated severe fibrosis / cirrhosis
 - EGD for esophageal varices
 - Abdominal ultrasound for HCC plus
 - Age-specific screening
 - Vaccination

NAFLD – NICE 2016 Guidelines

Assessment for NAFLD

- Identifying NAFLD in higher-risk groups
 - NAFLD more common in people with:
 - DMII
 - Metabolic syndrome
 - Group of chronic conditions that indicates increased CV risk including central obesity, insulin resistance or DMII, HTN and dyslipidemia
 - Take ETOH history to r/o ETOH-related liver disease
 - **DON'T** use routine liver blood tests to r/o NAFLD
- Diagnosing NAFLD in children (1-16 years old) and young people (16-18 years)
 - Offer liver U/S to test for NAFLD if they:
 - Have DMII or metabolic syndrome **AND** do not misuse ETOH
 - Refer children with suspected NAFLD to pediatric hepatology specialist in tertiary care
- Diagnose children / young people with NAFLD if:
 - U/S shows fatty liver **AND** other causes of fatty liver have been r/o
- Offer liver U/S to retest children / young people for NAFLD every 3 years if they:
 - Have normal U/S **AND** DMII or metabolic syndrome **AND** do NOT misuse ETOH



Assessment for advanced liver fibrosis in people with NAFLD

- Identifying people with advanced liver fibrosis
 - Offer testing for advanced liver fibrosis to people with NAFLD
 - Consider using enhanced liver fibrosis (ELF) test to test for advanced liver fibrosis
 - **DON'T** use routine liver blood tests to assess for advanced liver fibrosis
 - Diagnose people with advanced liver fibrosis if they have:
 - ELF score ≥ 10.51 **AND** NAFLD
 - Refer people diagnosed with advanced liver fibrosis to a hepatology specialist
- Explain to people with an ELF score <10.51 that:
 - They are unlikely to have advanced liver fibrosis **AND**
 - Reassessment q3 years for adults and q2 years for children / young people is sufficient **AND**
 - No interim tests needed
 - Give them advice about lifestyle modifications that they can make
- Offer retesting for advanced liver fibrosis for people with an ELF score <10.51 :
 - q3 years to adults and q2 years to children / young people
- Consider using ELF for retesting people with advanced liver fibrosis

Monitoring adults and young people for cirrhosis

- Monitor adults and young people with NAFLD and advanced liver fibrosis for cirrhosis (use NICE's cirrhosis guideline)

Extra-hepatic conditions

- Be aware that:
 - NAFLD is a risk factor for DMII, HTN, and CKD
 - In people with DMII, NAFLD is a risk factor for A. fib, MI, ischemic stroke, and death from CV causes

Lifestyle modifications for NAFLD

- Offer advice on physical activity and diet to people with NAFLD who are overweight or obese
- Explain to people with NAFLD that some evidence shows exercise reduces liver fat content
- Consider lifestyle interventions in NICE's obesity guidelines for people with NAFLD regardless of BMI
- **DON'T** offer omega-3-fatty acids because there isn't enough evidence to recommend their use
- Explain importance of staying within national recommended limits of alcohol consumption



People with NAFLD who are taking statins

- People with NAFLD taking statins should keep taking them
- Only consider stopping statins if liver enzymes double within 3 months of starting statins, including in people with abnormal baseline liver blood results

Pharmacological treatment

- In secondary or tertiary care settings only:
 - Consider **pioglitazone or Vitamin E for adults** with advanced liver fibrosis (regardless of whether they have diabetes)
 - Before prescribing pioglitazone or vitamin E, take into account their comorbidities and the risk of adverse events associated with these
- In tertiary care settings only:
 - Consider **Vitamin E for children** with advanced liver fibrosis (regardless of whether they have diabetes)
- In secondary or tertiary care settings only:
 - Consider **vitamin E for young people** with advanced liver fibrosis (regardless of whether they have diabetes)
- Offer to retest people with advanced liver fibrosis 2 years after they start a new pharmacological therapy:
 - Consider using ELF test to assess whether therapy is effective
 - If an adult's ELF test score has risen, stop either vitamin E or pioglitazone and consider switching to the other pharmacological therapy
 - If a child or young person's ELF test score has risen, stop Vitamin E

* Pioglitazone contraindicated in people with history of heart failure, previous or active bladder cancer and uninvestigated macroscopic haematuria

* At the time of publication (July 2016), neither pioglitazone nor vitamin E had a UK marketing authorisation for this indication. Prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented.

Recommendations for research

- Which non-invasive tests are most accurate and cost-effective in identifying NAFLD in adults with risk factors, DMII and metabolic syndrome?
 - NAFLD present in > 50% of adults with DMII or metabolic syndrome
 - Untreated NAFLD can progress to fibrosis, cirrhosis and HCC
 - Usually asymptomatic and detected incidentally on blood tests or abdo U/S (> 80% of patients with NAFLD have normal routine liver blood tests)
 - Need simple, accessible, cost-effective, non-invasive test to find NAFLD in huge # of at-risk people
 - 'Gold standard' for diagnosis = liver biopsy → not feasible in large #'s of at risk patients, so MR based techniques used in studies of non-invasive tests for NAFLD (MR techniques have high diagnostic accuracy but are impractical / expensive for large scale case finding)



- Which non-invasive tests most accurately identify NASH in people with NAFLD?
 - NASH only develops in minority of people with NAFLD → thought to be precursor of liver fibrosis, which is associated with morbidity and mortality
 - NASH is main target for treatment because reducing severity of NASH reduces risk of progressing to fibrosis and advanced liver disease
 - Only way to identify people with NASH is by performing an invasive liver biopsy (impractical given risks to health and cost)
 - Need simple non-invasive method for determining who has NASH
- Which non-invasive tests most accurately diagnose NAFLD and advanced liver fibrosis in children / young people?
 - NAFLD → most common chronic liver disease in children and young people in industrialised countries as a result of obesity
 - Spectrum of NAFLD (from simple steatosis to steatohepatitis, fibrosis, cirrhosis and liver-related morbidity) can be present in absence of abnormal liver tests → early detection and assessment of severity of NAFLD would help identify potential silent progressive fatty liver disease
 - One study shows some evidence for ELF in diagnosing advanced liver fibrosis in children and young people with NAFLD – Further research needed to confirm most accurate tests
- What is the clinical and cost effectiveness of probiotics / prebiotics to treat NAFLD in adults, young people and children?
 - Small body of evidence supports use of probiotics in NAFLD but data inconclusive → need high-quality double-blind randomised placebo-controlled trials
 - Cross-sectional studies suggest link between unfavourable disturbance in gut microbiota and obesity or DMII but limited evidence on influence of modifying gut microbiota on NAFLD
- What is the clinical and cost effectiveness of pharmacological therapy in children / young people with advanced liver fibrosis?
 - Observational studies report 10% of children / young people with NAFLD progress to advanced liver fibrosis and are at risk of developing advanced stages of liver disease
 - Pharmacological treatment (e.g., pioglitazone or vitamin E) can prevent progression as reported in a number of high quality studies in adults
 - Insufficient data on efficacy of similar pharmacological treatment in children / young people to make clear recommendations



Non-alcoholic Fatty Liver Disease (NAFLD) Including Liver Transplantation: AASLD / BSG / BASL / NHS Blood and Transplant Guidelines

Abbreviations: AASLD, American Association for the Study of Liver Disease; BASL, British Association for the Study of the Liver; BSG, British Society of Gastroenterology; NHS, National Health Services

Chalasani N, et al. Hepatology 2012; 55: 2005-23; Newsome PN, et al. Gut 2012; 61: 484-500.

- NAFLD
 - “Allowed” ongoing / recent modest weekly alcohol consumption and not diagnosing alcoholic liver disease
M < 21 d
F < 14 d
 - Excluded other causes / associations of NAFLD by liver biopsy
 - Perform liver biopsy when suspecting non-alcoholic steatohepatitis (NASH) / advanced fibrosis
 - Attempt weight loss through
 - Diet and exercise
 - Pharmaceuticals
 - Pre-diabetes
 - Metformin
 - Non-diabetic biopsy proven NASH
 - Pioglitazone use controversial
 - Vitamin E (α -tocopherol 800 IU/d) do not use in men with / at risk for prostate cancer
- } NAFLD / NASH plus co-existing conditions,
no data to support use of pioglitazone or vitamin E
- Bariatric surgery considered for
 - BMI > 40
 - BMI > 35 plus comorbidities
 - From the prospective of liver transplantation (LT) for NASH, the guideline authors suggest that the diagnosis must be made on
 - Clinical plus histopathological (biopsy) changes, or
 - ≥ 3 components of metabolic syndrome, plus the histological diagnosis of cryptogenic cirrhosis
 - Preoperative risk stratification
 - The usual criteria should be followed for allocation of an organ, such as the MELD score (e.g., list for LT if 5 yr survival after LT $\geq 50\%$)
 - A careful evaluation of CV risk must be performed, including 12-lead ECG plus echocardiogram to exclude
 - Acute heart failure
 - CP disease
 - Symptomatic valvular disease
 - Pulmonary hypertension
 - PAP > 25 mmHg
 - PCWP ≤ 15 mmHg
 - PVR ≥ 240 dyn/sec per cm^3



- Functional capacity
 - Maximum O_2 uptake on treadmill or
 - Metabolic equivalent of tasks (MET) ($MET < 4$; ≥ 1 intermediate risk factor)
 - Resting 1
 - Slow walking 2
 - Climbing 2 flights of stairs 4

Cardiology consultation

- Further cardiac testing
 - Dobutamine stress
 - Echocardiogram
 - Confirmatory angiography
 - Cardiopulmonary exercise test

AASLD

- Age > 50
- Smoker
- Past / family history of heart disease
- Diabetes

BSG-BASL-NHS

- Heart
 - Angina
 - Prior myocardial infarction
 - Heart failure
- CNS
- Kidney
 - Stroke / TIA
 - $Cr_s > 170 \mu\text{mol/L}$ ($> 2 \text{ mg/dL}$), or
 - Creatinine clearance $< 60 \text{ mL/min}$, or
 - Need for renal support
- Endocrine
 - Diabetes requiring insulin

- B-blockers (BB)
 - Already on non-specific BB (NSBB) for prophylaxis against bleeding esophagus varices $\rightarrow$ continue
 - Not already on NSBB $\rightarrow$ start cardioselective BB (e.g., bisoprolol) except when patient has refractory ascites, plus
- Statins
 - Pravastatin started $> 1 \text{ wk}$ before LT (do not use atorvastatin or simvastatin, due to cytochrome P450 isoenzyme interaction with calcineurins)
 - Note: AASLD – “until RCTs with histological endpoints prove their efficacy, statins should not be used to specifically treat NASH”
- Note
 - $MET \geq 4$, intermediate risk factors, no further cardiovascular testing necessary
 - ≥ 1 high risk factor, too high risk for liver transplantation



❖ High risk factors

- Heart
 - Acute heart failure
 - Acute coronary syndrome / ongoing ischemia
 - Symptomatic valvular disease
 - Pulmonary hypertension (significant)
 - Arrhythmias (significant)
- ↓
- Assess extent of obesity by calculating BMI after correction for ascites and peripheral edema ($\uparrow$ BMI $\rightarrow$ $\uparrow$ adverse outcome at 90 d post-LT)
 - Cirrhosis
 - Compensated
 - Attempt body weight loss pre-LT
 - Decompensated
 - Do not attempt weight loss due to $\uparrow$ risk of protein calorie malnutrition
- ↓
- Nutritional assessment and therapy, as appropriate
- ↓
- Bariatric surgery (at time of, or after LT) morbid obesity failed medical treatment of obesity retrotransplantation for recurrent NASH
- ↓
- Pre- / post-LT support
 - Emotional
 - Psychological
 - Educational
 - Spiritual
- ← ○ Use steroid-free immunosuppression, or early (within 3 mon) withdrawal of corticosteroids
- Post-LT
 - Monitor / control blood glucose (BE; 6 -10 mmol/L)
- ← ○ BE may be increased by immunosuppression with
 - Corticosteroids (CS)
 - Calcineurin inhibitor (CNI)
 - mTORi (mammalian target of rapamycin) inhibitors do not cause $\uparrow$ BMI, $\uparrow$ BP, $\uparrow$ lipids, DM or steatosis
- ↓
- Monitor of development / progression of

▪ $\uparrow$ weight	CS, CNI	▪ Diabetes	CS, CNI, mTORi
▪ Hypertension	CS, CNI	▪ Dyslipidemia	CS, CNI, mTORi
- ↓
- Protocol biopsy of liver allograft to diagnose and score severity of
 - Recurrent NASH
 - Additional / alternative diagnosis

Note: 1/3 of recurrent (allograft) NASH have normal LEs

- Continue to monitor / target
 - BMI < 25 kg/m², HgA₁C
 - Blood pressure 140 / 90
130 / 80 with DM +/- renal dysfunction
- Treat with CCB or ACE inhibitors

Abbreviations: ACE, angiotensin converting enzyme; BMI, body mass index; CCB, calcium channel blockers; CIN, calcineurin inhibitors; CP, cardiopulmonary; Cr_s, serum creatinine; CS, corticosteroids; DM, diabetes mellitus; LE, liver enzymes; mTORi, mammalian target of rapamycin inhibitors; NAFLD, non-alcoholic fatty liver disease; PAP, pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; RCT, randomized clinical trial; TIA, transient ischemic attack



EASL-EASD-EASO Clinical Practice Guidelines for the Management of NAFLD (Journal of Hepatology)

- NAFLD = excessive hepatic fat accumulation defined by steatosis in >5 % of hepatocytes
 - Associated with insulin resistance (IR)
 - Includes 2 distinct conditions with differential prognoses:
 - Non-alcohol fatty liver (NAFL)
 - Non-alcoholic steatohepatitis (NASH) (Spectrum → fibrosis, cirrhosis, and HCC)
 - Diagnosis requires exclusion of:
 - Secondary causes and daily ETOH consumption (>30 g/day in M and >20 g/day in F)
 - Definitive diagnosis of NASH requires a liver biopsy

RECOMMENDATIONS:

- Patients with insulin resistance and / or obesity / metabolic syndrome [MetS] should have diagnostic procedures to diagnose NAFLD
- Steatosis pts should be screened for secondary causes of NAFLD (note interaction b/w moderate ETOH use and metabolic risk factors in fatty liver)
- Identify coexisting chronic liver diseases which can lead to more severe liver injury

Prevalence

- Most common liver disease in Western countries – 17-46% of adults (parallel evidence of MetS syndrome)
- Also in 7% of normal weight / lean pts (usually younger F with normal liver enzymes)
- Need for NAFLD screening debated due to:
 - High direct / indirect costs of testing
 - Low predictive value of non-invasive tests
 - Risks of liver biopsy
 - Lack of effective treatments
- However NASH (esp advanced fibrosis) should be identified in at risk patients (age>50, DMII, or MetS) due to prognostic implications

RECOMMENDATIONS:

- Screen all patients with steatosis for MetS features (regardless of liver enzymes)
- Screen all patients with persistently abN liver enzymes for NAFLD (main cause of unexpected elevation)
- For obese patients with MetS, NAFLD screening w/ liver enzymes and / or U/S should be routine
- If high risk (age>50 years, T2DM, MetS) look for advanced disease (i.e., NASH with fibrosis)

Pathogenesis

- Weight gain / obesity and NAFLD linked to: high-calorie diet, excess (saturated) fats, refined carbs, sugar-sweetened beverages, high fructose intake and Western diet
- High fructose may increase risk of NASH and advanced fibrosis → ? confounded by excess calorie intake or unhealthy lifestyles / sedentary behaviour in NAFLD



RECOMMENDATIONS:

- Unhealthy lifestyles lead to development and progression of NAFLD → Assess dietary and physical activity habits as part of NAFLD screening
- Carriers of PNPLA3 I148M and TM6SF2 E167K variants have higher liver fat content and increased risk of NASH → NAFLD due to these variants is NOT associated with IR
- Do NOT routinely genotype (consider in selected patients / clinical studies)

Liver biopsy

- Essential for diagnosis of NASH → only procedure that differentiates NAFL from NASH
- NAFL encompasses:
 - Steatosis alone
 - Steatosis with lobular or portal inflammation WITHOUT ballooning
 - Steatosis with ballooning but WITHOUT inflammation
- NASH diagnosis requires:
 - Joint presence of steatosis, ballooning, and lobular inflammation
- “Burned-out NASH” = regression of advanced disease in pts exposed to metabolic risk factors
- NAFLD Activity Score (NAS) scoring system = use to assess disease severity once diagnosed
- Steatosis, activity and fibrosis (SAF) score = alternative with good reproducibility and more accurate / comprehensive description
- Fibrosis staging relies on the Kleiner classification

Aims of non-invasive assessment (can reduce need for liver biopsy):

- In primary care – identify risk of NAFLD in individuals with increased metabolic risk
- In secondary and tertiary care – identify those with worse prognosis, e.g., severe NASH
- Monitor disease progression
- Predict response to therapeutic interventions

RECOMMENDATIONS:

- U/S preferred 1st diagnostic procedure to image NAFLD – provides additional diagnostic info
- If imaging tools not available / feasible (e.g., large studies), serum biomarkers and scores are acceptable alternative to diagnose steatosis
- Quantitative estimation of liver fat only obtained by H-MRS (not recommended in clinical setting due to expense)



Steatosis

- Document whenever NAFLD suspected (predicts future DM, CV events and arterial HTN)
- U/S preferred to identify steatosis (widely available and cheaper than MRI which is gold standard)
 - U/S has limited sensitivity and doesn't reliably detect steatosis when <20% or if BMI >40
- Fatty liver index (FLI), SteatoTest, and NAFLD liver fat score = best validated steatosis scores → externally validated in general population or obese persons to predict metabolic, hepatic, and CV outcomes / mortality (scores predict presence NOT severity)
- Diagnosis of NASH provides prognostic info and indicates increased risk of fibrosis progression, cirrhosis, and possibly HCC → may also prompt closer f/u and need for more intensive therapy
- To date, non-invasive tests are not validated for diagnosis of NASH

RECOMMENDATIONS:

- NASH = only diagnosed by biopsy showing steatosis, hepatocyte ballooning and lobular inflammation

Fibrosis

- Most important prognostic factor in NAFLD (correlated with mortality)
- If advanced fibrosis = assess for biopsy
- NAFLD fibrosis score (NFS) and fibrosis 4 calculator (FIB-4) externally validated in ethnically different NAFLD populations, with consistent results
 - NFS, FIB-4, Enhanced Liver Fibrosis (ELF) and FibroTest predict overall mortality, cardiovascular mortality and liver-related mortality
 - Tests best at distinguishing advanced (PF3) vs non-advanced fibrosis (NOT significant (PF2) or any (PF1) fibrosis vs no fibrosis)
 - Negative predictive values (NPVs) for excluding advanced fibrosis > than positive predictive values (PPVs) → thus can use these non-invasive tests for 1st line risk stratification to exclude severe disease
- Imaging techniques – transient elastography performs better for cirrhosis (F4) than advanced fibrosis (F3)
 - Unreliable in presence of high BMI and / or thoracic fold thickness (use XL probe to reduce failure rate which remains high [35%])

RECOMMENDATIONS:

- Biomarkers, scores of fibrosis, and transient elastography = non-invasive procedures to identify cases of low risk of advanced fibrosis / cirrhosis
- Combo of biomarkers / scores and transient elastography = ? additional diagnostic accuracy → may reduce # of diagnostic liver biopsies and can be used to monitor progression
- Identification of advanced fibrosis / cirrhosis by serum biomarkers / scores and / or elastography is less accurate → need to confirm w/ biopsy according to clinical context
- If pt at high risk of liver disease progression → repeat liver biopsy after 5-year f/u



Common metabolic disorders related to NAFLD

- NAFLD closely linked to IR in liver, muscle, and adipose tissue and with MetS
- All components of MetS correlate with liver fat content, independently of BMI → presence of MetS = need to evaluate pt for risk of NAFLD

RECOMMENDATIONS:

- HOMA-IR (product of fasting glucose and insulin divided by 22.5) provides surrogate estimate of IR in non-diabetics
- In f/u HOMA-IR might identify patients at high risk of NASH / fibrosis progression
- Improved HOMA-IR w/ wt loss = ? sign of metabolic improvement (beneficial for NAFLD)

Obesity

- Obesity comorbidities (DMII, sleep apnoea, PCOS) drive NAFLD prevalence and severity
- Pts w/ BMI <30 (or even <25) but with visceral fat accumulation or dysfunctional adipose tissue can exhibit NAFLD with / without abnormal liver enzymes

RECOMMENDATIONS:

- F/u mandatory in obesity (increased risk of advanced disease)
- Most lean pts with NAFLD display IR and altered body fat distribution (even w/ less severe metabolic disturbance than overweight NAFLD) → still need f/u because of risk of progression

RECOMMENDATIONS:

- In pts with NAFLD, DM screening is mandatory, by fasting or random BG or HbA1c and if available by 75 g OGTT in high-risk groups
- In pts with DMII, look for NAFLD irrespective of liver enzyme levels, since DMII patients are at high risk of disease progression

Follow-up

- Incidental discovery of steatosis should lead to evaluation of family / personal history of NAFLD associated diseases and exclusion of secondary causes of steatosis (assess all MetS components)
- Calculate surrogate markers of fibrosis (NFS, FIB-4, ELF or FibroTest) for every NAFLD pt to r/o significant fibrosis:
 - If not able to r/o, refer to Liver Clinic for transient elastography
 - If confirmed → biopsy for final diagnosis
- Obese pts should be in a structured wt loss program and / or referred to obesity specialist
- All cases should receive CVD work-up and all DM pts should be referred to Diabetes Clinic



- Optimal f/u of NAFLD patients undetermined → Consider risk of progression of hepatic disease and underlying metabolic conditions as well as cost / workload for healthcare providers

Disease progression

- NAFLD generally progresses slowly but fibrosis rapidly progresses in 20% of cases
- Rate of progression corresponds to 1 fibrosis stage every 14 years in NAFL and every 7 years in NASH → Rate doubled by arterial hypertension
- NASH associated with increased standardized mortality ratio compared to general population
- US-diagnosed NAFLD not associated with increased mortality (? because progression to NASH and fibrosis is rare for steatosis alone)

RECOMMENDATIONS:

- NASH patients w/ fibrosis associated with HTN need monitoring due to higher progression risk

Cardiovascular disease

- Prevalence and incidence of CVD higher in NAFLD than matched controls (driven by association between NAFLD and MetS components)

RECOMMENDATIONS:

- CV complications frequently dictate outcome of NAFLD → CV system screening is mandatory in all pts (at minimum need detailed risk factor assessment)

RECOMMENDATIONS:

- Although NAFLD is risk factor for HCC (which may develop in pre-cirrhotic stage) risk is further increased by the presence of PNPLA3 rs738409 C>G polymorphism
- No recommendation currently about timing of surveillance and cost-effectiveness

Other extrahepatic disorders

- CKD found in 20-50% of NAFLD pts (particularly biopsy-proven NASH)
- US-defined NAFLD carries 1.5- to 2-fold adjusted risk of incident CKD in DMI
- NAFLD associated with CRC, metabolic bone disease (vit. D deficiency, osteoporosis) and rare metabolic diseases (lipodystrophies, glycogen storage diseases)

Treatment

- Successful treatment of NASH should decrease mortality and reduce progression to cirrhosis / HCC
- Resolution of histological lesions defining NASH accepted as surrogate endpoint
- Daily ETOH consumption up to 30 g (men) or 20 g (women) insufficient to induce ETOH steatosis and might even protect against NAFLD, NASH and fibrosis compared with total abstinence



RECOMMENDATIONS:

- NAFLD pts should be in structured program aimed at healthy diet and habitual physical activity
- Pts w/o NASH or fibrosis only need lifestyle counselling (no pharmacotherapy)
- In overweight / obese NAFLD, 7-10% body weight loss results in improvement of enzymes and histology
- Diet should restrict / exclude NAFLD-promoting components (processed foods, and high fructose intake) and macronutrients should be adjusted according to Mediterranean diet
- Both aerobic exercise and resistance training reduce liver fat → Tailor to patient preference

RECOMMENDATIONS:

- Pharmacotherapy reserved for NASH (Stage F2 or higher)
- Pts w/ less severe disease, but high risk of progression (i.e., DM, MetS, persistently increased ALT, high necroinflammation) could also be candidates to prevent progression
- Consider Pioglitazone (most efficacy data, but off-label outside DMII), Vit E (better short term safety and tolerability) or combo for NASH (no firm recommendations)
- Optimal treatment duration unknown
 - In patients with increased ALT at baseline = stop treatment if no reduction after 6 mon
 - In patients with normal ALT at baseline = no recommendations can be made
- Statins can reduce LDL-cholesterol and prevent CV risk, with no benefits / harm on liver disease

Iron depletion

- Hepatic iron accumulation associated with IR (iron depletion improves IR)
- In NAFLD, high ferritin levels common → have variable transferrin sat and independent of gene polymorphisms of familial hemochromatosis
- Phlebotomy to reduce iron stores to near iron deficiency improves NAS score w/o worsening fibrosis (more data needed)

RECOMMENDATIONS:

- Bariatric surgery reduces liver fat and likely reduces NASH progression → prospective data show improvement in NASH histology including fibrosis

Liver transplantation

- NAFLD cirrhosis = one of top 3 indications for transplant (3 and 5 yr survival unaffected)
- NAFLD = higher risk of death from CV complications and sepsis but graft failure risk is lower
- Mortality associated with BMI and DM (50% of cases w/ BMI >35 die w/i 1-year of transplant)
- Transplant failure (10% and 45% at 10 and 20 yrs) rarely assoc. w/ recurrent NASH cirrhosis (2%)

RECOMMENDATIONS:

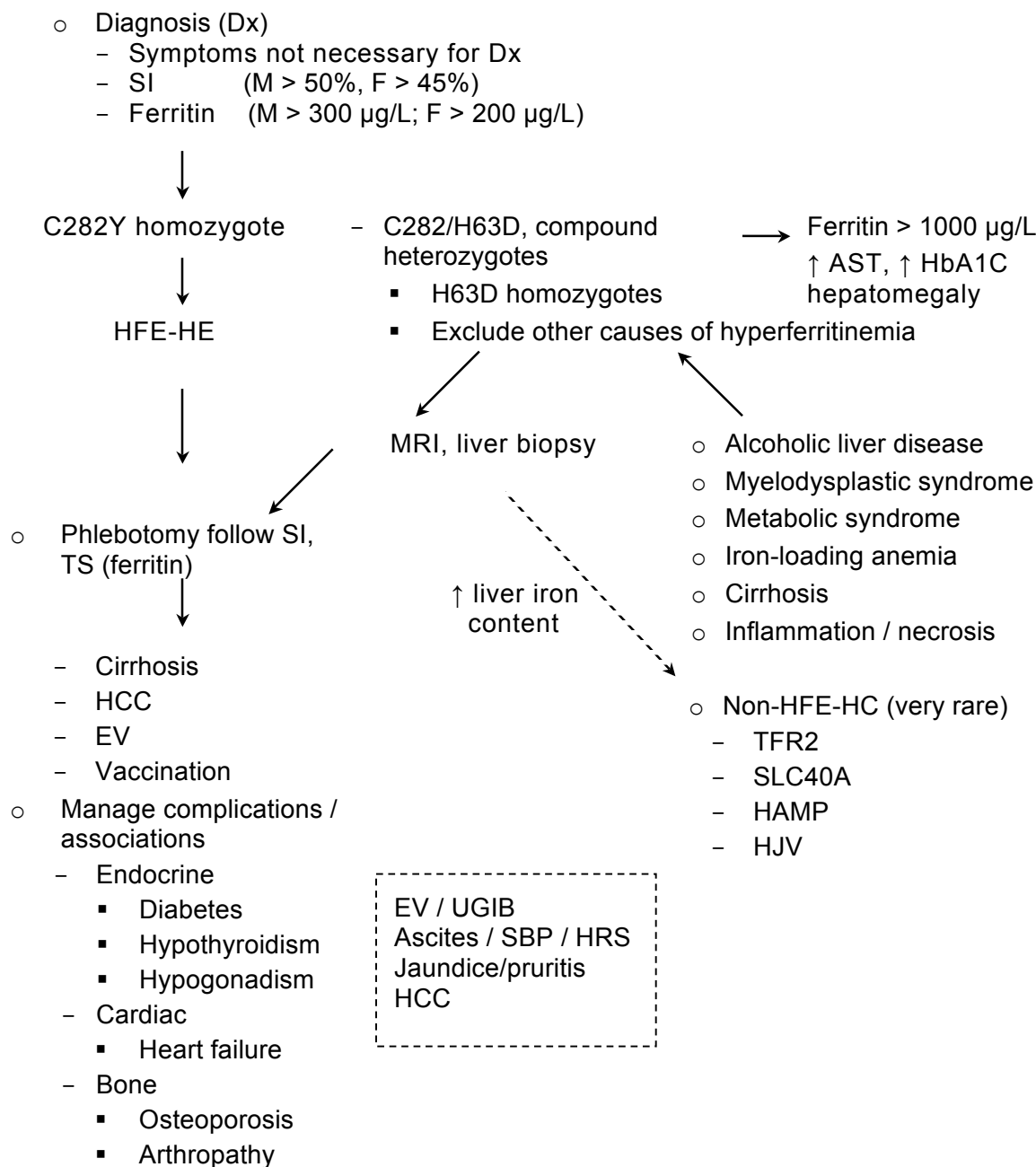
- Liver transplantation = accepted procedure in NASH pts with ESLD (comparable survival to other indications despite higher cardiovascular mortality)
- NASH pts with liver failure and / or HCC are candidates for transplant



HEREDITARY HEMOCHROMATOSIS (HH, aka HFE-HC): AASLD / EASL Guideline

Abbreviations: AASLD, American Association for the Study of Liver Disease; EASL, European Association for the Study of the Liver

Bacon BR, et al. Hepatology 2011; 54: 328-343; Please also see Pietrangelo A. Gastroenterology 2015; 149: 1240-1251; Sarigianni M, et al. Clin Gastroenterol Hepatol 2015; 13: 55-61; AASLD: Bacon BR, et al. Hepatology 2011; 54: 328-343; EASL: J Hepatology 2010; 53: 3-22.



Abbreviations: Dx, diagnosis; EV, esophageal varices; EV-UGIB, esophageal varices / upper GI bleed; HCC, hepatocellular cancer; HRS, hepatorenal syndrome; SBP, spontaneous peritonitis; SI, (iron) saturation index; TS, transferrin



WILSON DISEASE

➤ Definition

- A multisystem inherited disorder caused by mutations of the ATP7B gene on chromosome 13, which encodes ATP7B, a copper-transporting P-type ATPase in the trans-golgi network of hepatocytes which transports copper from the intracellular chaperone proteins into the secretory pathways for excretion of copper into bile and
 - Incorporation of copper into apo-ceruloplasmin for the synthesis of functional ceruloplasmin
 - The main tissues affected by excess accumulation of copper include the CNS, eye, liver, RBC and kidney

➤ Demography

- Prevalence depends upon organ affected, e.g., CNS (neurological symptoms ~ 3 / 10⁵)
- Usually presents between ages 5 to 35

➤ Clinical

❖ More common

- Eye
 - Copper deposited in the descemet membrane (Kayser Fleischer ring), forming a ring in the cornea (present in only 50%)
 - “Sunflower” cataracts
- CNS (neuropsychiatric)
 - Common
 - Ataxia
 - Tremor
 - Dystonia
 - Spectrum
 - Neurological
 - Psychiatric
 - Behavioural
- Liver
 - Acute / chronic liver disease spectrum
 - A notable (13%) cause of acute liver failure (ALF)
 - ALF F > M 4:1
- RBCs
 - Coombs-negative hemolytic anemia
- Kidney
 - Aminoaciduria
 - Nephrolithiasis / - calcinosis
 - Hypercalciuria
 - Acute renal failure

May precede CNS symptoms



❖ Less common

- Heart – Cardiomyopathy
 - GI – Pancreatitis
 - GU – Infertility
 - Miscarriages
 - Bone – Osteoarthritis
 - Chondrocalcinosis
 - Endocrine – Hypoparathyroidism
 - MSK – Myopathy
- Give the typical presentation of acute liver failure (ALF) due to Wilson disease.

- Demography – F > M 4:1
- Symptoms – Prominent jaundice
- Laboratory – ↑↑↑ bilirubin
- ↑ ALT / AST (transaminases)
- ↓ alkaline phosphatase (AP)
- ↓ hemoglobin
- ↓ cholinesterase

ALP/bilirubin < 4
 AST/ALT > 2.2
 100% sensitive and
 specific for ALF due to
 WD

SO YOU WANT TO BE A NEUROHEPATOLOGIST!

- Give a classification of the neurological abnormalities in Wilson disease.
 - Parkinsonism-like syndrome
 - Tremor-rigidity syndrome (aka juvenile parkinsonism)
 - Ataxia
 - Tremor (pseudosclerosis)
 - “wing beating”
 - Dystonia
 - Focal → severe → contractures
 - Drooling
 - Penjaw
 - Lip retraction
 - Speech (dysarthria)
 - Oropharyngeal dystonia



Clinical Pearls

- Jaundice in Wilson disease (WD) may be
 - Hepatocellular
 - Hemolytic
 - Mental confusion in WD may be
 - CNS WD
 - Hepatic encephalopathy
 - Severe cognitive decline is rare
 - In the pregnant woman with hemolysis and elevated transaminases
 - HELLP syndrome
 - Wilson disease
-
- About a third of persons with Wilson disease (WD) present with psychiatric abnormalities.
 - In children, these may include
 - Inappropriate behaviour e.g., sexual exhibitionism
 - Variable mood
 - Personality changes
-
- Give the typical psychiatric changes seen in adults with WD.
 - Depression
 - Paranoid
 - Psychosis, including schizophrenia
-
- Laboratory
- ❖ Serum ceruloplasmin
 - Compatible with diagnosis of WD when ↓ 50%
 - Interpretation must be influenced by false-positive (↓ ceruloplasmin) and false-negative (↑ ceruloplasmin) values
 - Heterozygotes for WD (in 20%)
 - ↓ ceruloplasmin

– Liver – Acute phase reactant – Estrogen	▪ Hepatitis ▪ Cholestatic disorders ▪ Infection ▪ Inflammation ▪ Rx ▪ Pregnancy
 - ❖ New-ceruloplasmin-bound copper (“free copper”)
 - Use for following effect of therapy, not for making diagnosis of WD
 - > 200 mcg / L suggests WD, but may also be caused by
 - Copper overdose (“intoxication”)
 - Liver disease
 - Acute liver failure (ALF)
 - Cholestasis



❖ 24-hr urine copper content

- Suggestive of WD
 - Asymptomatic children $> 0.64 \mu\text{mol} / 24 \text{ hr}$
 - Symptomatic including
 - Note ~20% of persons with WD have a 24-h urine copper $< 1.6 \mu\text{mol} / 24 \text{ hr}$
- $\uparrow$ urinary 24 hr copper is also observed in
 - Liver
 - Autoimmune hepatitis (AIH)
 - Chronic liver disease (CLD)
 - Acute liver failure (ALF)
 - Cholestasis
 - Heterozygotes (usually upper limit of normal [ULN])
- 24 hr urine copper excretion after D-penicillamine
 - Not recommended for use in adults
 - Performance characteristics depend upon cut-off values selected

❖ Hepatic copper concentration

- Patchy deposition of copper in hepatocytes leads to widely variable results
 - Not recommended for use in children
 - In adults $> 1.2 \mu\text{mol/g}$ dry liver weight
 - Sensitivity ~ 90%
 - Specificity ~ 95%
- Other causes of $\uparrow\uparrow$ hepatic dry weight copper concentration
 - Idiopathic copper toxicosis syndromes
 - Indian childhood cirrhosis

➤ Histopathology

- Wide spectrum of changes which may mimic
 - NALFD / NASH
 - Autoimmune hepatitis (AIH)
 - Chronic liver disease / cirrhosis
- Early changes
 - Fat
 - Micro- / macrovesicular
 - Glycogen
 - In nuclei
 - Necrosis
 - Focal hepatocellular
- Copper stains
 - Orcein
 - Rhodamine

} Lysosomal copper

Note: In WD the copper is in the hepatocytes, and is best determined by measurement of liver dry weight copper

“...hepatic copper overload cannot be excluded by histochemical evaluation of a liver biopsy alone”



SO YOU WANT TO BE A HEPATOLOGIST!

A person is suspected to have Wilson disease, and the serum ceruloplasmin is undetectable.

- Give the vital stain which should be used on the tissue obtained by liver biopsy.
 - The patient has a ceruloplasminemia, and will not accumulate copper in the liver and orcein or rhodamine stains for copper would be of no use.
 - A Prussian blue stain of the liver would reveal hemosiderosis.

➤ Diagnostic imaging

- Liver
 - Highly variable
 - Transcranial brain parenchyma sonography
 - Superior to MRI to detect early heterogeneity of lenticular nucleus
- CNS
 - MRI / CT of brain structure
 - Basal ganglia (“face of the giant panda” sign)
 - Thalamus
 - Brainstem
 - Lenticular nucleus
 - Central pons
 - Tectal plate
- Single-photo emission computed tomography
 - Early damage
 - Evaluating cognitive domain
- Special testing
 - Auditory evoked of brainstem
 - Monitor changes in function

➤ Genetic testing

- > 500 mutations in the Wilson gene (ATP7B gene)
- 380 mutations may be related to pathogenesis of WD
- Recommend genetic consultation for consideration of family testing includes pedigree analysis of “disease-associated” haplotypes
- Screening of 1st degree relatives
 - Likelihood
 - Heterozygote 0.25%
 - Homozygote 0.5%



Wilson Disease: EASL Guidelines

Abbreviation: EASL, European Association of the Study of the Liver

J Hepatology 2012; 56: 671-685.

➤ Leipzig Scoring System for Wilson Disease

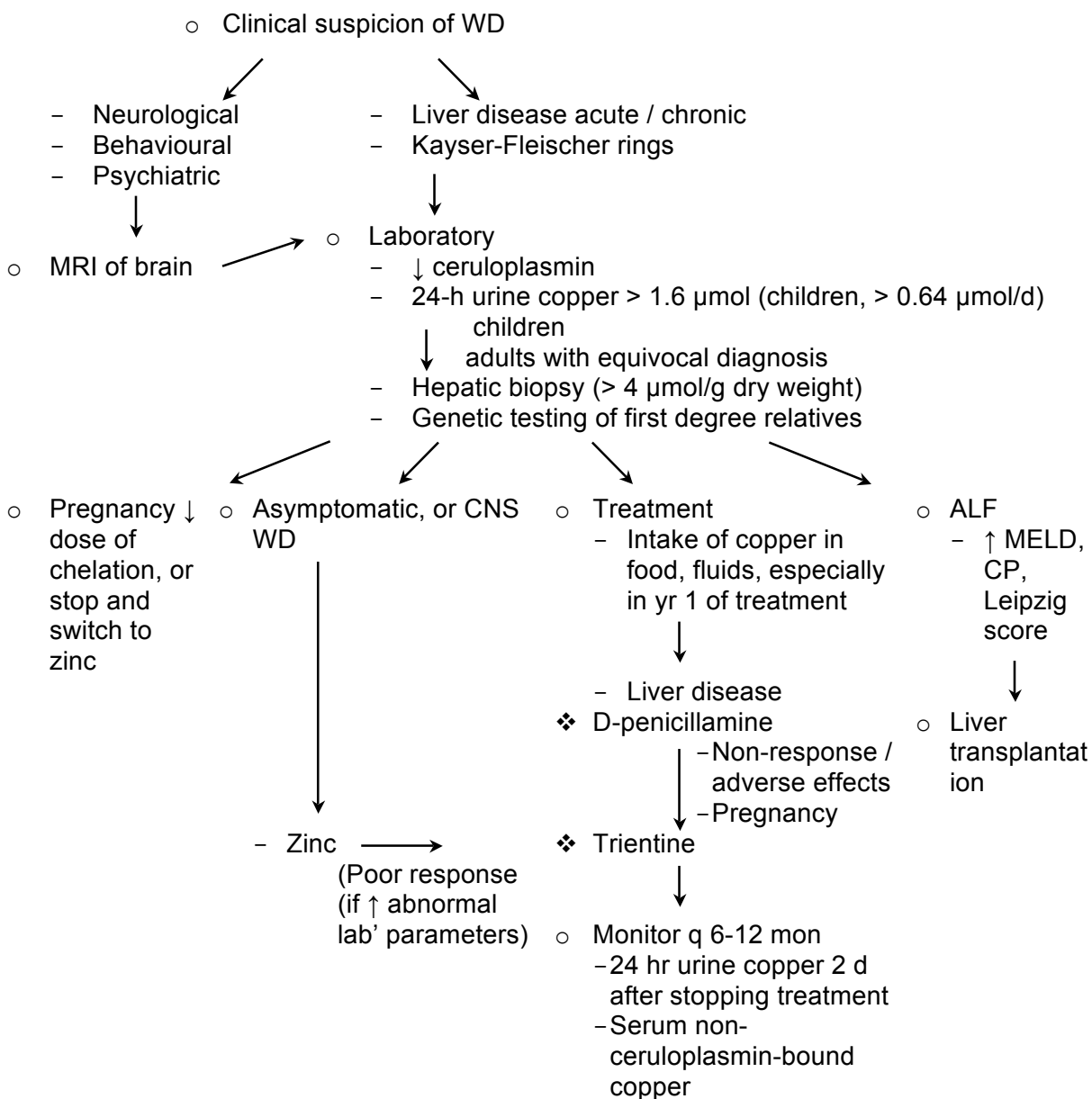
Scoring system developed at the 8th International Meeting on Wilson's disease, Leipzig 2001.

Typical Clinical Symptoms And Signs		Other Tests	
○ KF rings		○ Liver copper (in the absence of cholestasis)	
– Present	2	– > 5x ULN (> 4 µmol/g)	2
– Absent	0	– 0.8 - 4 µmol/g	1
○ Neurologic symptoms		– Normal (< 0.8 µmol/g)	-1
– Severe	2	– Rhodanine-positive granules	1
– Mild	1	○ Urinary copper (in the absence of acute hepatitis)	
– Absent	0	– Normal	0
○ Serum ceruloplasmin		– 1-2x ULN	1
– Normal (> 0.2 g/L)	0	– > 2x ULN	2
– 0.1 - 0.2 g/L	1	– Normal, but > 5x ULN after D-penicillamine	2
– < 0.1 g/L	2	○ Mutation analysis	
○ Coombs-negative hemolytic anemia		– On both chromosomes detect	4
– Present	1	– On 1 chromosome detected	1
– Absent	0	– No mutations detected	0
TOTAL SCORE		Evaluation	
≥ 4		Diagnosis established	
3		Diagnosis established	
≤ 2		Diagnosis very unlikely	

If no quantitative liver copper available, ** or typical abnormalities at brain magnetic resonance imaging. KF, Kayser–Fleischer; ULN, upper limit of normal.

Source: European Association of the Study of the Liver. J Hepatology 2012; 56: 671-685





❖ D-penicillamine

- Dose
 - 750-1500 mg/d po 1 hr ac
 - Children 20 mg/kg per day
 - Tolerability better starting at 250 mg/d
- Mechanism of action
 - ↓ cross-linking of collagen, with 250 mg ↑ dose per wk until max dose
 - Immunosuppression
- Excretion renal (urine)
 - Improvement of symptoms within 6 wk, except
 - ~1/3 of persons have ↑ (not ↓) in neurological symptoms, especially if high od
 - If d-penicillin stopped because of neurological AEs, do not restart → irreversible worsening



- Assessment of therapeutic effect
 - ↓ 24 hr urine copper (usually ~ 4 μ mol per day)
 - Stop d-penicillamine 2 d before assessing 24 hr copper
- Adverse effects (AEs) severe in 1/3, requiring d-penicillamine to be stopped

- Blood / bone marrow - CNS - Fever - Kidney - Lung - MSK - Skin - Skin	▪ WBC (PMCs) - ↓ platelets - Lymphadenopathy - Aplasia ▪ Retinitis ▪ ↓ taste ▪ Myasthenia gravis ▪ Polymyositis ▪ Proteinuria ▪ Hematuria ▪ Goodpasture syndrome ▪ Lupus-like syndrome (ANA-positive polymyositis) ▪ ↓ progeric changes - Pemphigus lesions - Lichen planis - Aphthous ulcers - Elastosis perforans serpingosa ▪ ↓ progression
- Give what contraception is recommended for women with WD.
 - Spermicide plus barrier, or
 - OCA
 - Only progesterone
- Give why **not** to use IUDs or estrogen-containing contraceptive in WD.
 - IUDs
 - May contain copper
 - Estrogen OCAs
 - ↓ biliary excretion of copper

Abbreviations: IUDs, intrauterine device; OCAs, oral contraception agents

Safety Alert

- Avoid use of d-penicillamine in pregnancy especially in first term (T1)
- Do not stop chelating therapy suddenly (↑ risk of ALF requiring LT)
- Avoid breastfeeding



❖ Trientine

- Pharmacology: a polyamine chelation of copper which increases its urinary excretion through its biotransformed metabolite, acetyltrien
- Dosing
 - 300 to 900 mg tid 1 hr ac or 3 hr pc, then 900 to 1500 mg/d maintenance
 - Children 20 mg/kg per day
- AEs
 - Less than with D-penicillamine
 - Less neurological worsening than with d-penicillamine
 - Blood
 - Iron chelation → sideroblastic anemia
- Monitoring
 - Measure 24 hr urine copper 2 d after stopping trientine

❖ Zinc

- Mechanisms of action
 - ↑ metallothion (MET)
 - Enterocyte
 - ↑ copper binding to MET → ↑ storage of copper in enterocyte → ↑ losses from sloughed cells
 - Hepatocyte
 - ↑ binding of copper → ↓ hepatotoxicity
- Dosing
 - 50 mg po tid
 - Children < 50 kg < body weight 25 mg tid

$\left. \begin{array}{l} \text{50 mg po tid} \\ \text{Children < 50 kg < body weight 25 mg tid} \end{array} \right\} \frac{1}{2} \text{ h ac}$
- Adverse effects
 - Hepatic decompensation
- Monitoring
 - 24 hr urinary copper
- Indications
 - Neurological WD (avoid in hepatic WD)

❖ Liver transplantation

- Patient survival (1 yr)
 - Indication
 - Acute liver failure (ALF) 73%
 - Chronic liver disease (CLD) 90%
- Graft survival 79%

➤ Prognosis

- With treatment
 - Liver
 - Function usually normalizes by 2 yr
 - ALF; fatal without liver transplantation usually
 - CNS
 - Symptoms
 - Usually lesser
 - May worsen
- Prognostic index for liver disease in WD (Nazer N, et al, modified by Dhawan et al.)
 - ≥ 11 is always fatal without liver transplantation
 - Based on AST, albumin, bilirubin, INR, WBC concentrations
 - For details, please see Liver Transplant 2005; 11: 441-448



PRIMARY BILIARY CHOLANGITIS (PBC): EASL GUIDELINES

Abbreviation: AASLD, American Association for the Study of the Liver Diseases; EASL, European Association for the Study of the Liver

EASL: J Hepatology 2017; 67: 145-172; AASLD: Lindor KD, et al. Hepatology 2009; 50: 291-308.

Note: The terminology for PBC has been changed from primary biliary cirrhosis to primary biliary cholangitis.

➤ Definition

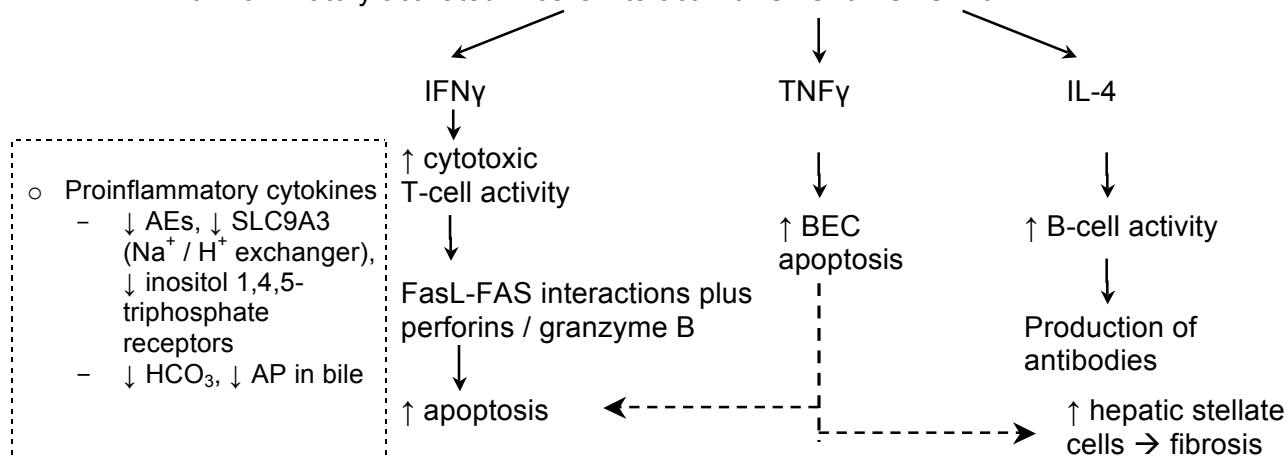
- A chronic, progressive, autoimmune, cholestatic liver disease associated with positive serology for antimitochondrial antibody or specific anti-nuclear antibody, and histopathological features of chronic non-suppurative, granulomatous, lymphocytic small bile duct cholangitis.
 - “cholestasis”: ↓ synthesis +/- flow of bile
 - Intrahepatic / extrahepatic
 - Hepatocytes / cholangiocytes
 - “chronic”: > 6 mon

➤ Demography

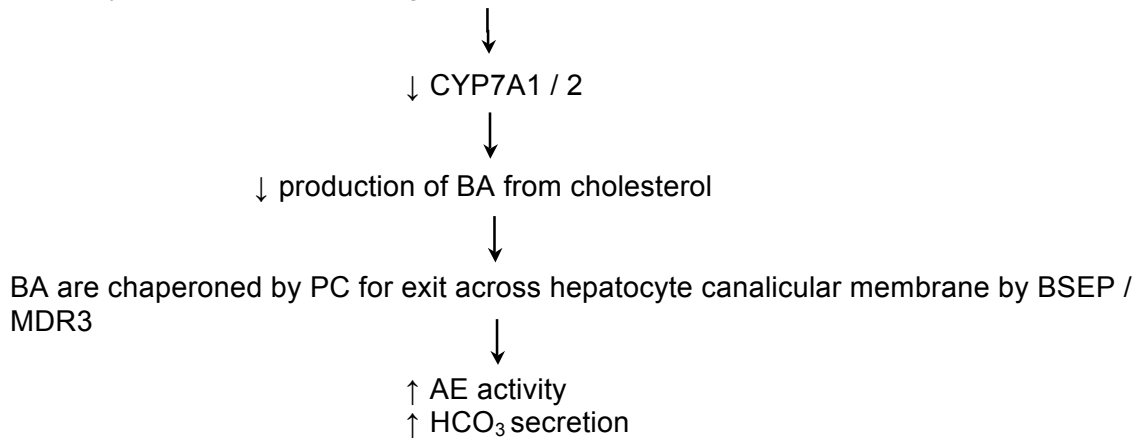
- F > M
- Incidence 1 – 2/10⁵
- Prevalence 100/10⁵ in females > 40 yr
- 10-yr survival rate in UDCA-treated non-transplanted patients ~80%

➤ Pathophysiology

- Immune injury to the biliary epithelium, leading to inflammation, fibrosis and cirrhosis
- Lymphocyte activation
 - B-cells activated by CD40 / CD40L
 - T- and B-cells interact → AMA specific to PDC-E2
- JAK-STAT, NFκB, PPAR
 - Macrophages and other immune cells activated by JAK-STAT, HLA locus and NFκB signaling → PPAR modulates (↓) NFκB
- Cytokines
 - Proinflammatory activated T-cells interact with CXCL9 / CXCL10



- T-cells
 - Cytotoxic → IFN γ → apoptosis
 - Th1
 - Th17
- Interact with CXCR3-CXCL10 / CCR6-CCL20 → ↓ immunological tolerance to biliary epithelial cells
- Apoptosis / fibrosis
- FXR / FGF-19
 - Ileocyte FXR / FGF-19 → ligate to FGFR4 / PPAR α/γ



- PC chaperone
- Anion exchanger (AE) / HCO₃ secretion

What goes wrong in PBC:

- ↓ AEs / ↓ HCO₃ →
 - ↑ adenylyclase
 - Unchaperoned BA
 - ↓ BSEP (cholestasis) → ↑ CD40, ↑ CXCL10, ↑ HLA-DR → Apoptosis → ↑ fibrosis inflammation cholestasis
 - ↓ PDC-E2

Abbreviations: AE, anion exchanger (Cl⁻ / HCO₃⁻); AMA, anti-mitochondrial antibody; BA, Bile acid; BSEP, bile salt export protein; FAS / FASL, CD95 / CD95 ligand; FGF19, fibroblast growth factor; FGFR4, fibroblast growth factor receptor 4; FXR, farnesoid X receptor; HLA, human leukocyte antigen; JAK-STA, Janis-kinase / signal transducer and PPAR; NFkB, nuclear factor kappa-light-chain enhancer of activated B cells; PBC, primary biliary cholangitis; PC, phosphatidylcholine; PDC-E2, pyruvate dehydrogenase complex E2 subunit

➤ Causes / associations

- Idiopathic, immune mediated
- May be caused by or associated with the use of drugs
 - Antibiotics
 - Amoxicillin / clavulanic acid
 - Trimethoprim / sulfamethoxazole
 - Anabolic steroids
 - Immunosuppressants
 - Azathioprine



- Genetic
 - Transporter genes ABCB4 / ABCB11
 - ATP8B1
 - Clinical syndromes
 - (BRIC)
 - Low phosphate associated cholelithiasis (LPAC) syndrome
 - MYO5B (villin) or FXR
 - Progressive familial intrahepatic cholestasis type 1-3
 - Persistent hepatocellular secretory failure (PHSF)
 - Intrahepatic cholestasis of pregnancy (ICP)
- Recurrent urinary tract infections
- Smoking
- Clinical
 - Fatigue and pruritis (50%)
 - Jaundice
 - Associated complications
 - Ascites
 - Spontaneous bacterial peritonitis (SBP)
 - Hepatorenal syndrome (HRS)
 - Esophagogastric variceal bleeding (EGVB)
 - Hepatic encephalopathy (HE)
 - Hepatocellular cancer (HCC)
 - Coagulopathy
 - Deficiency of fat soluble vitamins
 - Metabolic bone disease
 - Steatorrhea
- Diagnostic imaging
 - Causes of cholestasis (other than PBC)
 - Focal lesions, cirrhosis, ↑ portal vein diameter / flow
 - Splenomegaly, ascites
 - Curiosity
 - Chest X-ray
 - Hilar lymphadenopathy
- Laboratory
- ❖ Biochemistry
 - Cholestasis
 - ↑ alkaline phosphatase (AP)
 - ↑ gamma glutanyl glutarate (GGT)
 - ↑ bilirubin
 - ↑ ALT / AST (transaminases)
 - ↑ IgM (↑ IgG in AIH-PBC overlap syndrome)
 - ↑ Cholesterol (HDL)



- Cirrhosis
 - ↓ albumin
 - ↑ INR
 - ↓ platelets

Time sequence $\uparrow$ GGT $\rightarrow$ $\uparrow$ AP $\rightarrow$ ALT / AST $\rightarrow$ $\uparrow\uparrow$ AST / ALT > 1

SO YOU WANT TO BE A GASTROENTEROLOGIST!

- Give the exception, in the setting of PBC of when $\uparrow$ bilirubin does not suggest advanced fibrosis/cirrhosis.
 - $\uparrow$ bilirubin does not indicate the presence of cirrhosis in ductopenic non-cirrhotic variant of PBC

- Predictors
 - Cholestasis
 - Ductopenia
 - Progression
 - Hepatitis / necrosis
 - $\uparrow$ ALT, AST
 - Fibrosis
 - $\uparrow\uparrow$ AST, $\uparrow$ ALT, AST / ALT > 1
 - Cirrhosis
 - $\uparrow$ INR, $\uparrow$ bilirubin, $\downarrow$ albumin, $\downarrow$ platelets
 - Anti-centromere
 - Portal hypertension phenotype

❖ Serology

- Anti-mitochondrial antibody (AMA; positive in 90% of PBC)
 - Targets E2-subunit of pyruvate dehydrogenase complex (PDC)
- Give a clinical as well as genetic and an immunological laboratory test in which the level of the AP does not reflect the extent of the hepatic cholestasis (“false-positive”)
 - Clinical
 - Acute hepatic injury
 - Genetic
 - Secretor of ABO blood group antigens
 - Immunological
 - IgG concentrations (in AIH-PBC overlap syndrome)
 - ANA
 - PBC-specific antinuclear antibodies (anti-SP100, anti-gp210)
 - Perinuclear rim
 - Nuclear dot
 - Anti-centromere (predicts $\uparrow$ portal pressure)

➤ Histopathology

- Lymphocytic cholangitis
 - $\uparrow\uparrow$ periductal T lymphocytes, macrophages, eosinophils causing epithelioid granulomatous and disruption of the bile duct epithelium (aka “florid bile duct lesion”)



- ↑ lymphocytic infiltration
 - Portal tract
 - ↑ ductopenia (IHC positive for keratin 7) } Marginal ductular reaction
 - Interface hepatitis
 - Periportal hepatocytes
 - Focal emperiopolesis
 - Nodular regenerative granules
 - Orcein-positive granules
 - Cirrhosis
 - Micronodules
 - Septa wide / fibrosis halozones
- Give the histopathological staging system for PBC.
- | | | Inflammation | Duct Reaction
(ductopenia) | Fibrosis | Cirrhosis | Orcein-positive
Granules |
|------|----------|--------------|-------------------------------|----------|-----------|-----------------------------|
| 1967 | Scheuer | + | + | + | + | |
| 1978 | Ludwig | + | + | + | + | |
| 2010 | Nakanuma | | + | + | | + |
- Give indications for liver biopsy in the patient with clinical features and serology suggestive of PBC.
 - Clinical
 - Clinical suspicion of PBC but absent PBC-specific antibodies (AMA, ANA)
 - Overlap syndrome suspected
 - PBC+AIH
 - PBC+NASH
 - Comorbidities
 - Systemic / extrahepatic
 - Biochemical
 - Poor response to UDCA (inadequate decline in AP and total bilirubin)
 - ↑ HVP, and lack of HVP on UDCA
 - Give the features on liver biopsy / histopathology which predict a poor prognosis in PBC.
 - ↑↑ lymphocytic interface hepatitis
 - ↓↓ bile ducts (↑↑ ductopenia)

Abbreviations: HVP, hepatic venous pressure gradient; NASH, non-alcoholic steatohepatitis; UDCA, ursodeoxycholic acid

➤ Suggested Investigative Pathway

- Suspect
 - Fatigue / pruritis
 - Signs of liver disease
 - Laboratory
 - ↑ AP / GGT, ↑ ALT / AST, ↑ IgM



- Diagnosis
 - Laboratory
 - AMA > 1:40, ANA (PBC specific)
 - Anti-gp20, anti-sp100
 - Biopsy
 - Not always necessary
 - Genetic studies, if indicated
- Liver dysfunction / prognosis
 - Laboratory
 - ↑ bilirubin, ↑ INR, ↓ platelets
 - ↓ albumin
- Risk stratification
 - Laboratory
 - As above, plus
 - Anti-centromere

Recommendations regarding diagnosis

- Take a detailed history and physical examination when evaluating patients with biochemical tests that suggest cholestatic liver disease (III, 1).
 - Associated diseases: autoimmune Hashimoto thyroiditis, Sjogren disease / sicca, celiac disease, systemic sclerosis.
 - IBD not a/w PBC (PSC).
 - History of intensive care therapy or polytrauma linked with secondary sclerosing cholangitis.
 - Environmental exposure to paint, diesel, oil and gas linked with IgG4 cholangitis.
- Order ultrasound as the first line non-invasive imaging procedure in order to differentiate intra from extra hepatic cholestasis (III, 1).
 - All patients should have an U/S to exclude mechanical bile duct obstruction, mass lesions and abnormalities of gallbladder.
 - In PBC expect normal liver morphology. In advanced disease, can see features of chronic liver disease: focal liver lesions, portal hypertension, splenomegaly, ascites.
- Perform serologic screening for AMA and PBC-specific-ANA in all patients with unexplained cholestasis (III, 1).
 - AMA specific and sensitive for unexplained cholestasis but not 100% specific for PBC (only 1/6 with + AMA and normal ALP develops PBC in 5 years)
 - PBC specific ANA anti-sp100, anti-gp210
- Perform extended imaging by MRCP in patients with unexplained cholestasis. EUS can be an alternative to MRCP for evaluation of distal biliary disease (III, 1).
- Consider liver biopsy after serologic screening and extended imaging, in patients with ongoing unexplained intrahepatic cholestasis (III, 1).
- Consider genetic tests for inherited cholestatic syndromes in patients where clinical appropriate (III, 1).
 - Progressive familial intrahepatic cholestasis type 1-3, persistent hepatocellular secretory failure, intrahepatic cholestasis of pregnancy, Alagille syndrome
- In adult patients with cholestasis and no likelihood of systemic disease, dx of PBC can be made if elevated ALP and AMA titre > 1:40 (III, 1).
 - >90% of PBC patients are AMA positive
 - Patient with AMA positivity and normal liver enzymes, should have follow up with annual biochemical reassessment of liver enzymes.



- A dx of AMA negative PBC can be made in patients with cholestasis and positive specific ANA immunofluorescence (sp100, gp201) (III, 1).
 - Useful in 5-10% of AMA negative PBC cases
- EASL Recommends against liver biopsy for dx of PBC, unless PBC-specific antibodies are absent, co-existent AIH or NASH is suspected, or other usually systemic comorbidities are present (III, 1).
 - Histology shows chronic, non-suppurative inflammation, destruction of interlobular and septal bile ducts, termed 'florid duct lesions'.
 - Later in disease, get ductopenia, inflammation and collagen deposition (fibrosis).

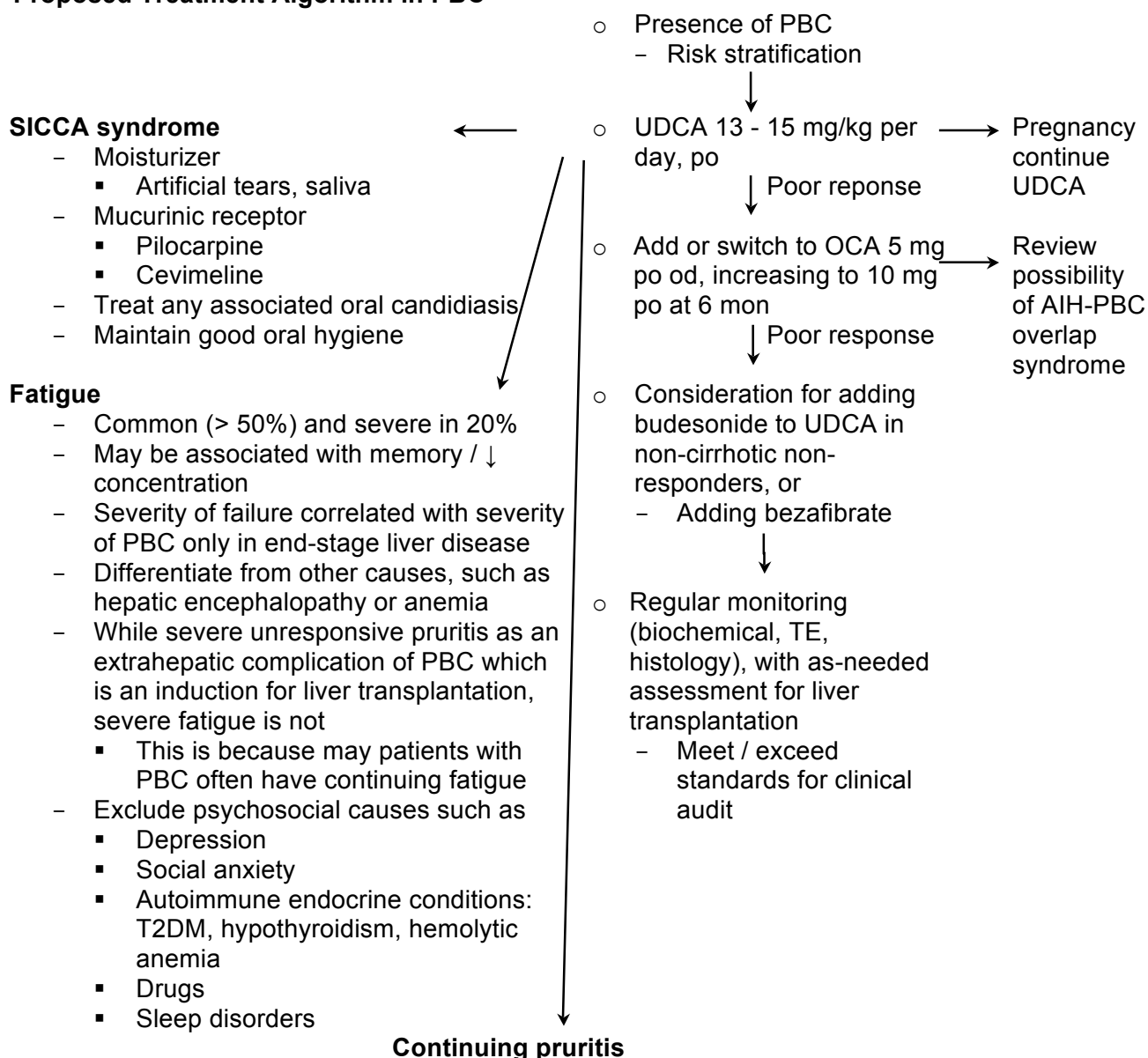
➤ Stratification of risk

- Recommendations regarding risk stratification
 - Recognize that patients at greatest risk of complications from PBC are those with inadequate biochemical response to therapy and cirrhosis (II2, 1).
 - Strongest RF for inadequate biochemical response to therapy is early age at diagnosis (age <45) and advanced stage at presentation (III, 1).
 - Male sex a/w later dx and more advanced disease at presentation, poor biochemical response to treatment and higher risk of HCC.
 - PBC-specific ANA more observed in patients with severe PBC with an unfavourable course
 - Evaluate all patients for stage of disease using a combination of non-invasive tests (Bilirubin, ALP, AST, Albumin, platelet, elastography) at baseline and during follow up.
 - Risk scores such as GLOBE and UK-PBC recommended
- Give the features of the patient with PBC who is at risk of serious disease, with poor response to standard therapy and appropriate doses of ursodeoxycholic (UDCA).
 - Patient
 - Age < 45 yr
 - Males
 - Symptoms
 - Biochemistry
 - Progressive jaundice due to progressive icteric cholestasis
 - ↑ bilirubin plus albumin blood concentrations
 - Antibody positive for sp100 and gp120 antigens
 - Fibrosis score
 - Model for end-stage liver disease (MELD)
 - Enhanced liver fibrosis (ELF) score
 - Serum concentrations of
 - Hyaluronic acid
 - Procollagen III peptide
 - Tissue inhibitor of metalloproteinase
 - Aspartate aminotransferase (AST)-to-platelet ratio index (APRI)
 - Unvalidated tests under study-cytokeratin 18
 - Wisteria floribunda agglutinin-positive MAC-2 binding protein (WFAT-M2BP)
 - Scoring symptoms Mayo risk score
 - Transient elastography (TE; aka vibration-controlled transient elastography)



- Therapy
 - Response (biochemical) to treatment with UDCA
 - Useful marker of PBC progression when $\uparrow$ TE ($\uparrow$ liver stiffness, due to fibrosis)
 - TE > 9.6 kPa suggest 5x $\uparrow$ risk of decompensation
 - Liver transplantation
 - Mortality
- Scoring systems of poor response to UDCA in PBC
 - Types qualitative (binary) e.g., Paris-criteria (requires histological stage-specific threshold for biochemical markers such as AP, ALT, AST, GGT, bilirubin, INR)
 - continues (qualitative) e.g., UK-PBC or Globe scoring systems (older approach)
 - Evaluation at 6 - 12 mon of UDCA treatment helps to select PBC patients to switch from UDCA to obeticholic acid (OCA) selective for farnesoid X receptor (FXR; please see pathophysiology of PBC)

Proposed Treatment Algorithm in PBC



Ursodeoxycholic Acid (UDCA)

- Mechanism of action
 - UDCA → ↑ post-translational signaling → ↑ trafficking of transport proteins / channels into the appropriate membranes in hepatocytes and cholangiocytes → cytoprotective / anti-apoptotic / immunosuppressing effects (some bile acids are proinflammatory at low concentrations, and ↑ apoptosis / necrosis at high concentrations)
- Adverse effects
 - Baldness
 - Flatulence / diarrhea
 - ↑ body weight
 - 20% of patients stop therapy due to intolerance to UDCA
- Optimal responders
 - Total serum bilirubin > 68 $\mu\text{mol/L}$. +/-
 - Stage I / II liver histology at start of UDCA
- Benefits
 - ↓ need for liver transplantation
 - ↓ mortality
 - ↓ progression from stage I to II / IV (7% vs 35%)
 - ↑ likelihood of removing at early stage PBC at 4 yr (29% vs 76%)
 - ↓ risk of developing esophageal varices (EV) at 4 yr (16% vs 58%; no difference in bleeding EV)
 - ↓ risk of developing ascites, jaundice
 - ↑ transplant-free survival

	5	10	15
- UDCA	90%	78%	66%
- Non-UDCA	79%	59%	32%

Obeticholic Acid (OCA)

- Selective for farnesoid receptor (FXR)
 - directly alters expression of genetic induced in all parts of bile acid metabolism
 - ↑ expression of FGF-19, as well as other GI peptides
- Used alone or added to UDCA in PBC patients with poor response to UDCA
 - AP > 1.67x ULN, +/-
 - Total bilirubin ↑ <2x ULN
- Adverse effect may ↑ pruritis → OCA stopped in ~5% of PBC patients



Budesonide

- Synthetic corticosteroids with high first-pass metabolism in the GI tract and liver, resulting in low bioavailability (< 20%), and therefore much lower risk of adverse effects than, prednisone, for example.
- Synergistic effect to ↑ expression of AEs when budesonide is combined with UDCA (“add-on therapy”)
- Improvement of AP as well as hepatic histology
- Mechanism of action
 - ↓ interface hepatitis
 - ↑ AE2 expression (beneficial to biliary epithelium)

Bezafibrate: Not currently recommended based on meta-analysis

- A fibrate with anti-cholestatic benefits
 - ↑ peroxisome proliferator-activated receptor (PPAR)
 - ↓ bile acid synthesis
 - ↓ CYP2C9
- Used as 400 mg po per day, with UDCA
- Benefits
 - ↓ AP
 - ↓ pruritis
 - ↓ mortality (trend)
 - ↑ interval free of
 - Decompensation
 - Transplantation
- Associations
 - Preconception counselling and preventive care for EGV
 - UDCA
 - For PBC
 - Cholestyramine
 - For itch

} Safe in pregnancy

“The function of education is to teach one to think intensively and to think critically. Intelligence plus character – that is the goal of true education.”

Martin Luther King Jr.



Primary Biliary Cholangitis (PBC): AASLD Guidelines

Abbreviation: AASLD, American Association for the Study of the Liver Diseases

Lindor KD, et al. Hepatology 2009; 50: 291-308.

- Suspect middle age female with fatigue, pruritis, cholestatic blood tests (↑ AP, ↑ GGT), AMA-positive; signs of cirrhosis
- Diagnosis ≥ 2 of these 3
 - ↑ AP, ↑ GGT
 - AMA-positive
 - Liver biopsy
 - Non-suppurative destructive cholangitis
 - Destruction of interlobular bile ducts
- ↓
- Treatment
 - PBC: Ursodeoxycholic acid (UDCA, 13-15 mg/kg per day)
 - Indication: PBC with abnormal LE
 - Steatorrhea
 - Fat soluble vitamin supplement
 - Calcium 1500 mg/d plus vitamin D 1000 IU/d
 - Osteoporosis (BMI / DEXA scan follow-up)
 - Pruritis
 - Skin emollients
 - Anti-histamines
 - ↓
 - Cholestyramine (up to 4 gm qid po)
 - Rifampin (150-300 mg bid; monitor ALT, AP, bilirubin), or
 - Naltrexone (up to 50 mg/d), or
 - Phenobarbital (90 mg q hr), or
 - Sertraline (75-100 mg/d)
 - ↓
 - Sicca syndrome
 - Eyes, mouth – artificial tears / saliva
 - ↓
 - Pilocarpine, cevimeline
 - ↓
 - Cyclosporine ophthalmic emulsion
 - Artificial saliva
 - Vagina
 - Moisturizers
 - Estrogen cream
 - Sjögren syndrome (CREST) / Raynaud disease
 - GI complications of involvement
 - Dysphagia
 - SIBO
 - Wide-mouthed colonic diverticula

○ Liver transplantation (note UNOSRRB approved MELD points for intractable pruritis)



- Follow up
 - LE, LFTs
 - If cirrhosis
 - Esophageal varices
 - EGD q 1-3 yr
 - Hepatic encephalopathy
 - Hepatocellular cancer
 - Ultrasound q 6 mon
 - DEXA scan (osteoporosis)
 - Avoid hepatotoxic / renotoxic drugs

Abbreviations: AASLD, American Association for the Study of the Liver Diseases; CREST, Calcinosis, Raynaud, esophageal dysfunction sclerodactyly lelangiectasia; LE, liver enzymes; SIBO, small intestinal bacterial overgrowth; UDCA, ursodeoxycholic acid

Treatment Alert

- Give the name of the drug which when given by mouth is relatively contraindicated in persons with portal hypertension / cirrhosis and esophageal varices.
 - Alendronate

Recommendations regarding treatment

- All patients with PBC should receive oral UDCA at 13-15 mg/kg/day (single or divided dose as tolerated) as first line therapy, usually continued for life (I, 1).
 - Very safe, minimal side effects of weight gain (~3kg in first 12 months, hair thinning, rarely diarrhea and flatulence)
 - Not teratogenic, safe during pregnancy and lactation
- Consider use of OCA + UDCA combination therapy in patients with inadequate response to UDCA or OCA mono therapy if intolerant to UDCA. Initial dose OCA of 5 mg, titrate to 10 mg to tolerability at 6 months.
 - In a phase III study, patients on UDCA with ALP > 1.67 x ULN and/or bilirubin elevated < 2x ULN received OCA as add-on therapy. Study showed biochemical improvement but survival benefit is yet to be demonstrated.
 - Major side effect is dose dependent exacerbation in pruritic, limiting its use.
- EASL recommends expert consultation for all pregnant patients to guide therapy, noting that pregnancy is typically well tolerated in non-cirrhotic patients with PBC.
- Continue UDCA in pregnancy, even though supporting data are limited. Pruritus management is important and may require specialist advice (III, 1).
 - Cholestyramine and rifampicin (third trimester onwards) are safe.
 - Rarely, plasmapheresis may help severe unbearable itch.
- EASL has no recommendations regarding budesonide and bezafibrate use in combination with UDCA as results of RCT are not published yet. •



Recommendations regarding AIH-PBC overlap disease

- PBC may present with additional features of AIH in 10% of cases, most often simultaneously, but sometimes sequentially even years after diagnosis of PBC.
- Prognosis of PBC-AIH overlap is worse than PBC alone and patients usually present with more advanced fibrosis.
- Liver biopsy is mandatory in confirming features of AIH-PBC overlap, and should be considered in patients with disproportionate elevation in ALT and / or IgG (III, 1).
- For patients with PBC-AIH overlap, EASL suggests immunosuppressive treatment in patients with severe interface hepatitis and it should be considered in those with moderate interface hepatitis.

Recommendations regarding symptom management

- Pruritis:
 - Treat pruritis using a stepwise approach. Patients with severe pruritis may have an aggressively ductopenic variant of PBC, with a poor prognosis. Refer these patients to an expert centre.
 - Use emollients and oat meal extract to improve dry and inflamed skin
 - Use cold water for baths and showers
 - Psychologic intervention for addictive scratching / scratch dependence
 - Search for added allergens, especially in patients with associated hypereosinophilia or IgE mediated allergy
 - Use cholestyramine as first line agent for pruritis.
 - Administer 2-4 hrs before or after other medications to avoid interference with other medications
 - Use Rifampicin as a second line therapy for pruritis at a dose of 150-300 mg daily. • Risk of hepatotoxicity, hemolysis and INR elevation. Monitor serum liver tests, CBC and Coags after initial use (at 6 and 12 weeks) and following dose increase • Oral opiate antagonists (naltrexone and nalmefene) are sometimes used as third line therapy. SSRIs, gabapentin, antihistamines are other options (little evidence, not included in recommendations)
 - Fatigue:
 - There is no pharmacological agent to improve fatigue. Must seek and treat associated and alternate causes of fatigue, especially anemia, hypothyroidism and sleep disturbances (III, 1).
 - Advise patients with fatigue to develop coping strategies, including avoidance of social isolation, which can compound effects of fatigue.
- Sicca:
 - Sicca complex is common in PBC. Consider referral to expert clinicians (III, 1).
 - Artificial tears, saliva, vaginal moisturizer and estrogen creams
 - Pilocarpine and cevimeline (Muscarinic receptor agonist)
 - Oral hygiene to prevent dental caries
 - Risk of oral candidiasis



Recommendations regarding complications of liver disease

- Osteoporosis:
 - Consider risk of osteoporosis in all patients with PBC (III, 1).
 - Use DEXA at presentation and at follow up in 1-5 years where indicated (III, 1).
 - Supplement patients with calcium and Vitamin D according to local practice (III, 2).
 - Bisphosphonates are safe and effective treatments for patients with PBC who have an elevated fracture risk from osteoporosis but use with caution in those with varices (consider parenteral options in this case).
- Malabsorption
 - Fat soluble vitamin malabsorption can happen in patients with PBC, especially in those with prolonged jaundice. Supplementation should be considered on an individual basis (III, 2).
- Hyperlipidemia:
 - Hyperlipidemia is a feature of cholestasis but there is no substantial evidence for an elevated CVS risk in patients with PBC. Consider treatment in those with concomitant classical CVS risk factors as per normal practice.
- Cirrhosis:
 - Follow HCC surveillance protocol as per separate EASL guidelines (III, 2).
 - Consider patients for transplant when they present with complications of cirrhosis, markers of disease severity (e.g., persistent elevated bilirubin values) or MELD >>15, or severe medically resistant pruritis. Listing for transplant should follow local guidelines (II-2, 1).
 - In patients with proven or likely recurrent PBC post transplant, use of UDCA is safe and can improve liver biochemistry.

"The art of being wise is the art of knowing what to overlook."

William James



AIH-PBC Overlap Syndrome

➤ Demography

- May occur separately or together

➤ Diagnosis

- The diagnostic criteria for AIH-PBC are different from those for AIH or PBC when they occur alone
 - At least 2 of these in each group
 - PBC-related
 - AP > 2x ULN, or GGT > 5 ULN
 - AMA > 1:40
 - Hepatic histology florid bile duct lesion plus ≥ 2 of the following
 - AIH-related
 - ALT > 5x ULN
 - IgG > 2x ULN, or SMA-positive
 - Hepatic histology ≥ moderate interface hepatitis
 - Presence of additional antibodies
 - SLA / LP
 - dsDNA

Histopathology Alert

- Interface hepatitis occurring in PBC is often associated with ↑ risk of progression/poor prognosis

Clinical Diagnostic Alert

- In the patient with AIH in whom the AMA becomes positive, while you think about the possible AIH-PBC overlap syndrome, remember that acute hepatitis which may result from the AIH may ↑ AMA, with hepatic histology not supporting that overlap diagnosis.

➤ Treatment

- AIH-PBC have an ↑ risk of poor prognosis
- Use UDCA plus azathioprine +/- corticosteroids
- Standard preventive measures for corticosteroids / azathioprine
- Monitor bone mineral density (BMD) by DEXAScan
- Liver transplantation for the usual indications of decompensation, plus intractable pruritis

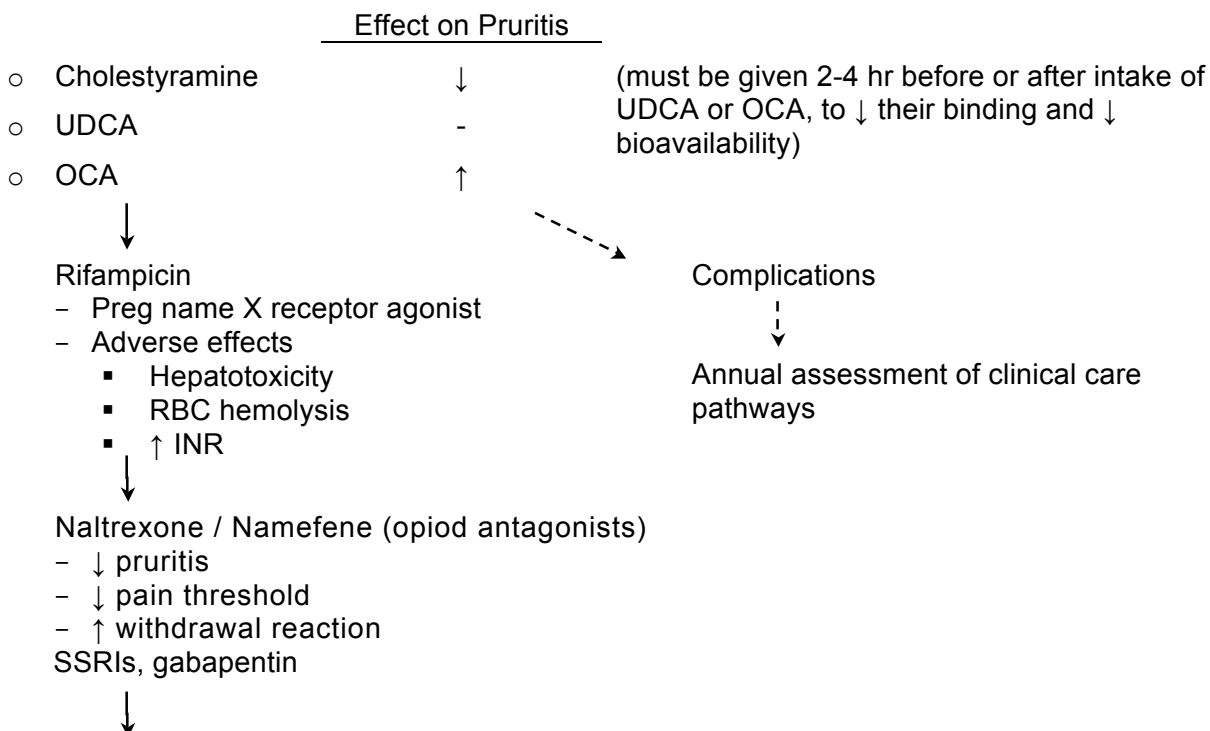


Pruritis

❖ General

- Emollients, oatmeal baths, cold water baths
- Search for possible allergens
- Psychological care for “addictive / dependent scratching”

❖ Pharmacological



❖ Others

- Nasobiliary drainage
- Molecular absorbance recirculating system
- Ultraviolet (UV) light therapy

❖ Liver transplantation for end-stage PBC, or for intractable pruritis

Complications of PBC

❖ Raynaud Phenomenon

- ~ 10% of PBC patients (CREST syndrome)
- White-blue-red changes in skin colour in the cold
- Avoid the cold
- Vasodilator



❖ Osteoporosis

- Calculate fracture risk (WHO FRAX score: <http://www.shef.ac.uk/FRAX>)
- Calcium, vitamin D, bisphosphonates, sunshine, exercise, ↓ smoking, hormone replacement therapy (HRT)

MCQ Trick

- Give the use of the type of bisphosphonate to be used in the patient with advanced chronic liver disease who requires a bisphosphonate for DEXAScan demonstrated ↓ bone mineral density (BMD).
 - Use a parenteral rather than an oral bisphosphonate to avoid direct damage to associated esophageal varices.

- Provide fat-soluble vitamin supplementation when appropriate, especially for chronic cholestasis / jaundice.

MCQ Trick

- Give the concentration of cholesterolemia which must be treated with a statin in patients with PBC.
 - In PBC, the total cholesterol is usually the result of
 - ↑ HDL
 - ↑ lipoprotein X
 - Component of LDL
 - This, the hyperlipidemia associated with PBC does not usually need to be treated

} Anti-pathogenic

❖ Esophageal varices (EV)

- In early PBC, there is nodular regenerative hyperplasia (NRH), so portal hypertension and its complications may develop in the pre-cirrhotic stage.
 - This precirrhotic esophageal varices
 - Occur in 6% of PBC patients
 - Are high-risk EV
- Give the risk factors for esophageal varices (EV) in PBC which indicate a high risk for bleeding.
 - General
 - Males
 - ↓ albumin (< 4 g/dL)
 - ↑ INR
 - ↑ bilirubin (> 1.2 mg/dL)
 - ↓ platelets (< 140 – 200 x10⁹ cells / L), +/-
 - Mayo PBC risk score ≥ 4.5
 - Specific (for EVB in PBC): Baveno-IV guideline
 - Platelets < 150 x 10⁹ cells/L
 - LSM ≥ 20 kPa



- Screen / surveillance for EV

Abbreviations: LSM, liver stiffness measurements; Pa, Pascal units



- ❖ Hepatocellular Carcinoma (HCC)
 - More common in PBC
 - ↑ histological grade on presentation
 - More common in UDCA-nonresponders
- ❖ Liver transplantation
 - Indication
 - ↑ total bilirubin > 50 - 85 $\mu\text{mol/L}$ (> 3.5 mg/dL) → perform
 - Mayo PBC score, or → assess for possible liver transplantation
 - MELD score
 - Prognosis
 - 5 yr survival 80 - 85%
 - Be aware that pruritis may become worse post-LT
 - Complications
 - Follow post-LT PBC patients for other associated autoimmune conditions
 - Recurrence of PBC after LT may be asymptomatic and liver biochemistry may be normal, so must be followed with scheduled liver biopsy (histological changes of de novo PBC > 20%)
 - Post-LT recurrence of PBC may be common, but is usually
 - Mild
 - Responds well to UDCA
 - Does not usually progress to requiring repeat LT

Quality Care!

- Give the personal audit features which should be assessed q 1 yr, adherence to quality care and compliance with clinical practice guidelines.
 - Diagnosis
 - Confirm correct diagnosis of PBC
 - Suspect possible development of PBC-AIH overlap syndrome, and perform liver biopsy for histopathology
 - Risk stratification and annual monitoring of biochemical measures of liver enzymes / function
 - Look for complications such as osteoporosis, esophageal varices, HCC
 - Vaccinations kept up-to-date
 - Treat with UDCA 13 - 15 mg po od confirm patient adherence
 - Assess for possible liver transplantation



PRIMARY SCLEROSING CHOLANGITIS (PSC): ACG / AASLD CLINICAL PRACTICE GUIDELINE

Abbreviations: ACG, American College of Gastroenterology; AASLD, American Association for the Study of Liver Diseases

Lindor KD, et al. Am J Gastroenterol 2015; 110: 646-59; and Chapman R, et al. Hepatology 2010; S1: 660-78; Rizvi S, et al. Clin Gastroenterol Hepatology 2015; 13: 2152-2165; and Eaton JE, et al. Gastroenterology 2013; 145: 52: 521-536.

➤ Definition

- “.... An idiopathic condition defined as the presence of beading and stricture formation of the intra and / or extrahepatic bile ducts that cannot be ascribed to another cause....”

➤ Causes

- Cholangitis
 - Secondary
- Choledocholithiasis
 - IgG4-associated
- Tumour
 - Cholangiocarcinoma
 - Papillary tumour
- Immune
 - AIH / PBC
- Infection
 - HIV
- Inherited
 - Histiocytosis

➤ Diagnosis

- MRCP demonstrating characteristic beading / strictures in bile ducts
 - ERCP with antibiotic prophylaxis, plus balloon dilation and short term stenting for severe stricture
 - ↓
 - Cytology biopsies and FISH, to exclude cholangiocarcinoma in dominant stricture (> 1.5 mm in CBD, and > 1.0 mm in HD)
 - Exclude secondary causes
 - Liver biopsy only needed to diagnose small duct PSC, or
 - Exclude other conditions which overlap or mimic PSC (i.e., causes of secondary SC)
 - Because of possible overlap syndromes with AIH and PBC, test for AMA, ANA, ASM and IgG

“Let’s change the interactions between alerting, orienting and executive functions, and control in a standard curing paradigm.”

Grandad



➤ Treatment

- Avoid doses of UDCA > 28 mg/kg per day
- Caution in using UDCA for PSC plus UC (↑ risk of CRC)



○ Cirrhosis management - Esophageal varices ▪ EGD q 1-3 yr - Hepatic encephalopathy - Ascites, SBP - HCC ▪ US q 6 mon - Vaccinations - Cholangitis ↓ - Decompensated cirrhosis ↓ - Liver transplantation ▪ UNOSRRB approved MELD exception points ▪ Cholangitis -> 2 episodes of bacteremia -> 1 episode of sepsis ▪ Cholangiocarcinoma < 3 cm, no metastases, clinical trial ▪ Intractable pruritis	○ Screening and Surveillance - Surveillance with MRCP or ultrasound cross-sectional imaging, plus CA 19-9 q 6-12 mon - Ultrasound of gallbladder ▪ Polyps → cholecystectomy ↓ ▪ PSC and IBD ↓ ▪ Presence of UC / CC ↓
- Colonoscopy q 1h with CRC screening biopsies

Abbreviations: AIH, autoimmune hepatitis; AMA, anti-mitochondrial antibody; ANA, anti-nuclear antibody; ASM, anti-smooth muscle antibody; CBD, common bile duct; CC, Crohn colitis; CRC, colorectal cancer; ERCP, endoscopic retrograde cholangiopancreatography; FISH, fluorescence in-situ hybridization; IBD, inflammatory bowel disease; MELD, Model for End-stage Liver Disease; MRCP, MR cholangiopancreatography; PBC, primary biliary cirrhosis; PSC, primary sclerosing cholangitis; SBP, spontaneous bacterial peritonitis; UC, ulcerative colitis; UNOSRRB, United Network for Organ Sharing Regional Review Board; US, abdominal ultrasound



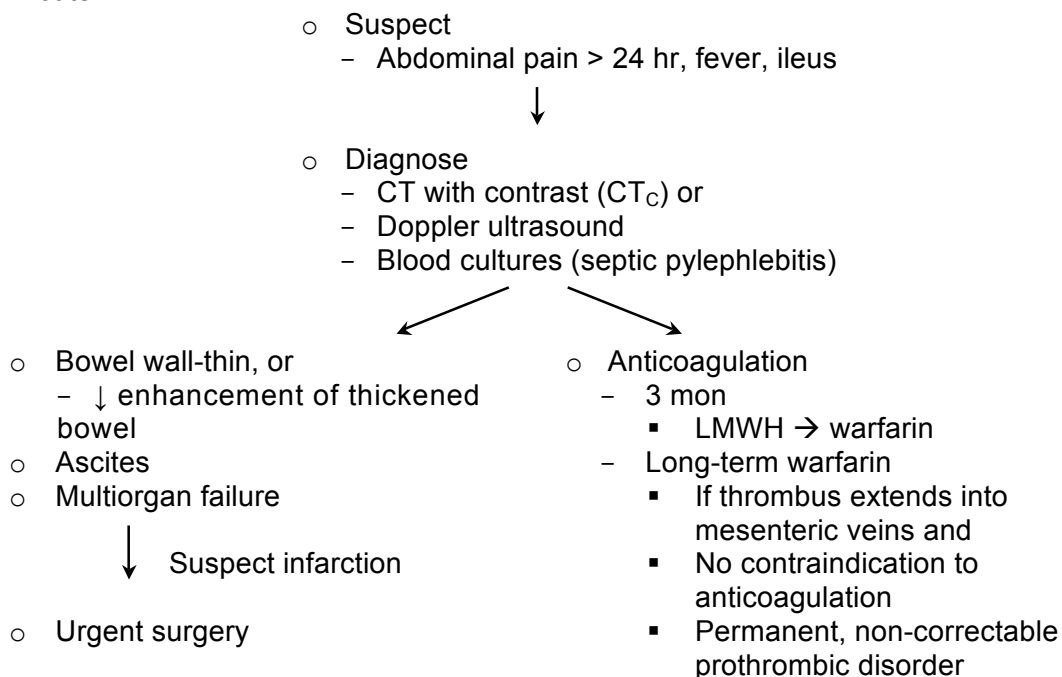
VASCULAR DISORDERS OF THE LIVER: AASLD CLINICAL GUIDELINES

Abbreviations: AASLD, American Association for the Study of Liver Diseases

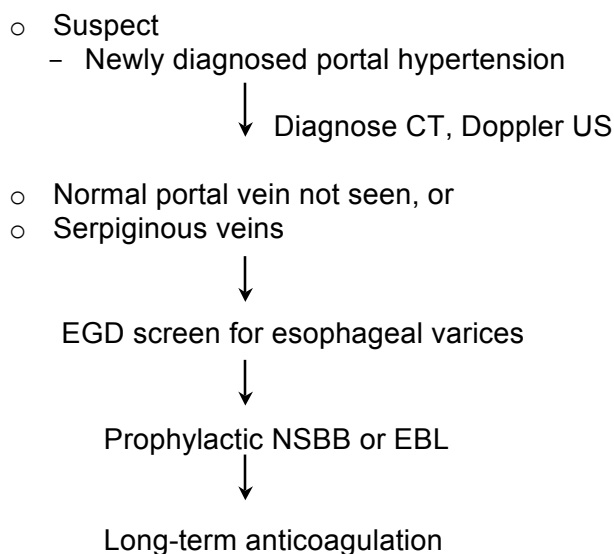
DeLeve LD, et al. Hepatology 2009; 49: 1729-64.

Portal Vein Thrombosis (PVT)

❖ Acute



❖ Chronic



Abbreviations: CT, CT scan with contrast; EBL, esophageal band ligation; EGD, esophagogastroduodenoscopy; LMWH, low molecular weight heparin; NSBB, non-specific beta-blocker



Sinusoidal Obstruction Syndrome (SOS; aka Hepatic Venocclusive Disease): AASLD Guidelines

Abbreviations: AASLD, American Association for the Study of Liver Diseases

DeLeve LD, et al. Hepatology 2009; 49: 1729-64.

- Suspect within 3 wk of HSCT
 - High dose chemotherapy drugs, or
 - Chemotherapy plus total body irradiation, in setting of hematopoietic stem cell transplantation (HSCT), plus
 - Liver
 - Tender
 - Painful
 - Ascites
 - > 2-5/lbs weight gain from fluid
 - Bilirubin
 - > 34.2 $\mu\text{mol/L}$
 - Doppler ultrasound
 - Transvenous liver biopsy plus HVPG > 10 mmHg (specificity > 90%, PPV > 85% for SOS)
- ```

graph TD
 A[Transvenous liver biopsy plus HVPG > 10 mmHg] --> B[Where possible, switch from hepatotoxic treatments (↓ radiation dose, D / C cyclophosphamide)]
 A --> C[Fluid overload]
 C --> D[Diuretics, paracentesis, hemofiltration, hemodialysis]
 D --> E[If good prognosis for underlying condition requiring HSCT]
 E --> F[Liver transplantation]

```
- Where possible, switch from hepatotoxic treatments (↓ radiation dose, D / C cyclophosphamide)
  - Fluid overload
    - Diuretics, paracentesis, hemofiltration, hemodialysis
  - If good prognosis for underlying condition requiring HSCT
  - Liver transplantation

Note – TIPS, tissue plasminogen activator, or defibrotide not recommended

Abbreviations: HSCT, hematopoietic stem cell transplantation; HVPG, hepatic vein pressure gradient; PPV, positive predictive value; TIPS, transjugular intrahepatic portosystemic shunt

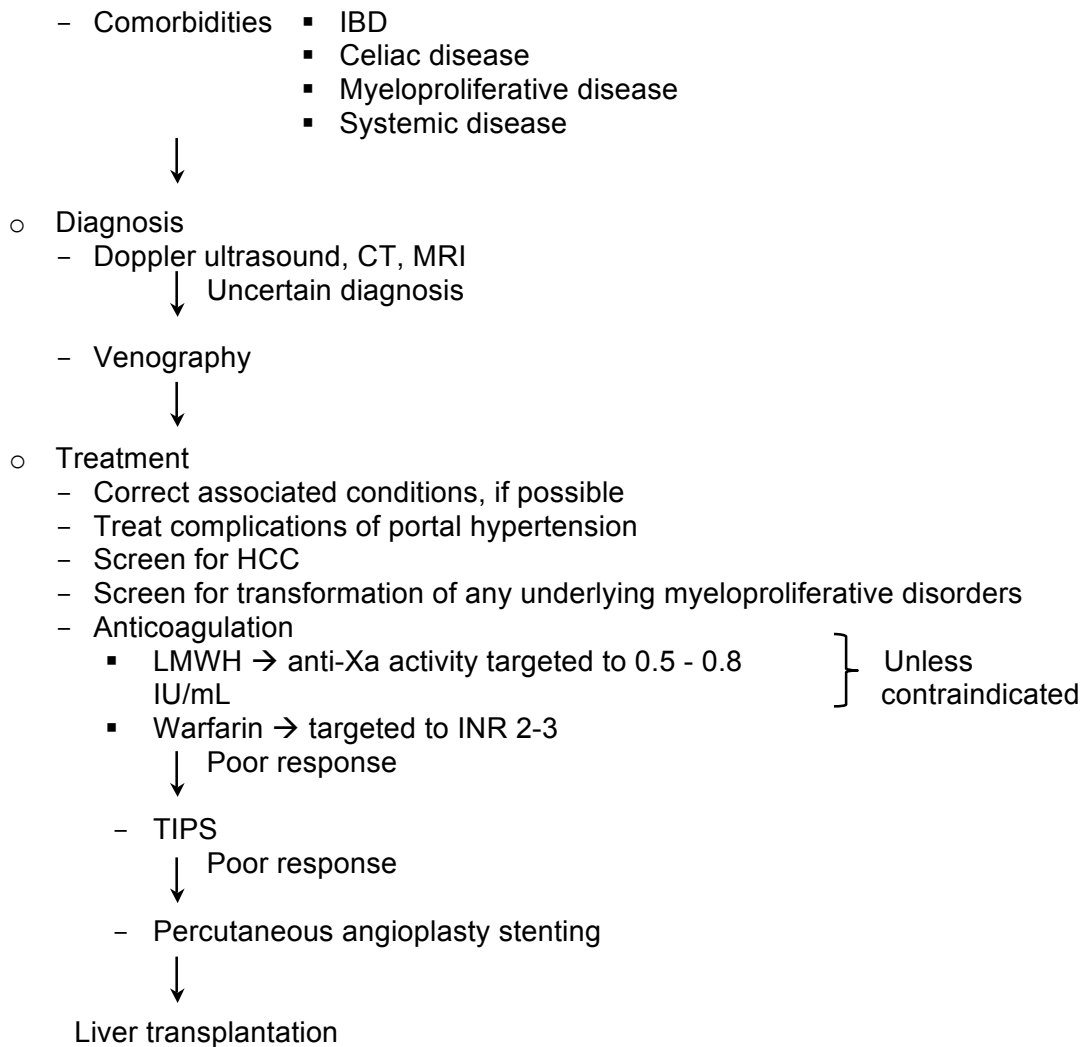
## **Budd-Chiari Syndrome (BCS)**

DeLeve LD, et al. Hepatology 2009; 49: 1729-64.

### ➤ Definition

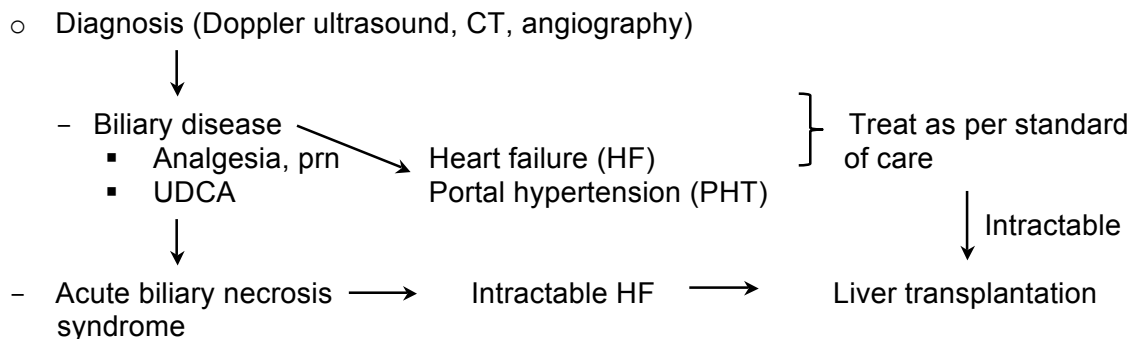
- Obstruction of the hepatic venous (HV) outflow tract, independent of the level or mechanism of HV obstruction, but not including sinusoidal obstruction syndrome (SOS), or cardiac / pericardial diseases.
- Suspicion
  - Liver
    - Liver disease
    - Upper abdominal pain, ascites, hepatomegaly
    - Thrombophilia
    - Distention of abdominal wall
    - Veins (IVC obstruction)





**Hereditary Hemorrhagic Telangiectasia (HHT) (aka Rendu-Osler-Weber [ROW / OWR] disease)**

DeLeve LD, et al. Hepatology 2009; 49: 1729-64.



Abbreviations: prn, as necessary; UDCA, ursodeoxycholic acid



## HBV INFECTION: EASL GUIDELINES

EASL Clinical Practice Guidelines. J Hepatology 2017; 67(2): 370-398.

Abbreviations: EASL, European Association for the Liver

### ➤ Virology

- Hepadnaviridae family
- Small, enveloped, primary hepatotoxic DNA viruses
- Genome
  - 3.2 kb, partly double-stranded, relaxed-circular (RC) DNA
  - 4 open reading frames which encode
    - HBeAg secreted dimeric protein
    - HBcAg viral capsid protein
    - HBV polymerase, reverse transcriptase (Pol / RT) activity
    - PreS1 / PreS2 / HBsAg large, medium, small surface envelop glycoproteins
    - HBV regulator of transcription
- HBC in blood → HBV nucleocapsid → nucleus → release of RC DNA → Nucleoplasm → conversion to cccDNA wrapped in histones → episomal chromatinized structure (transcription template) → capsid protein viral polymerase
  - Infectious virions
    - 9 genotypes plus subtypes
  - Non-infectious subviral particles
- Viral clearance
  - B cells → neutralizing antibodies
  - T-cells → anti-viral cytokines
    - T cells dysfunction virus-specific and global
    - INTS10 gene activated IRF3 → anti-virus interferons

Abbreviations: cccDNA, covalently closed DNA; RcDNA, relaxed circular DNA

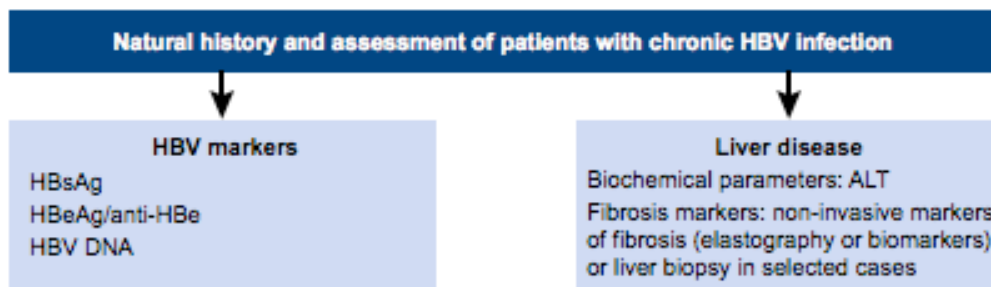
### ➤ Terminology

| Old                        | New                      |
|----------------------------|--------------------------|
| ○ Immune tolerant          | HBeAg+ Chronic Infection |
| ○ Immune reactive, +       | HBeAg+ Chronic hepatitis |
| ○ Inactive carrier         | HBeAg- Chronic infection |
| ○ HBeAg- chronic hepatitis | HBeAg- Chronic hepatitis |





Natural history and assessment of patients with chronic HBV infection based upon HBV and liver disease markers



|                 | HBeAg Positive    |                                | HBeAg Negative               |                                  |
|-----------------|-------------------|--------------------------------|------------------------------|----------------------------------|
|                 | Chronic Infection | Chronic Hepatitis              | Chronic Infection            | Chronic Hepatitis                |
| HBsAg           | High              | High / intermediate            | Low                          | Intermediate                     |
| HBeAg           | Positive          | Positive                       | Negative                     | Negative                         |
| HBV DNA         | $> 10^7$ IU/mL    | $10^4 - 10^7$ IU/mL            | $< 2000$ IU/mL <sup>°°</sup> | $> 2000$ IU/mL                   |
| ALT             | Normal            | Elevated                       | Normal                       | Elevated*                        |
| Liver disease   | None / minimal    | Moderate / severe              | None                         | Moderate / severe                |
| Old terminology | Immune tolerant   | Immune reactive HBeAg positive | Inactive carrier             | HBeAg negative chronic hepatitis |

\*Persistently or intermittently. HBV DNA levels can be between 2,000 and 20,000 IU/ml in some patients without signs of chronic hepatitis.

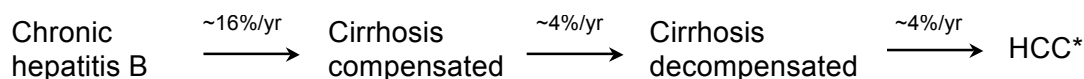
Printed with permission: EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. J Hepatology 2017; 67(2): 370-398, Figure 1.

- Give the reason why persons who have HBeAg+ chronic HBV infection are at risk of developing HCC in the precirrhotic phase ("immune tolerant").
  - The level of HBV DNA is high ( $> 10^7$  IU/mL), and the HBV DNA becomes
    - Integrated HBV DNA, with
    - Persistence of cccDNA, "inactive carrier"
    - Clonal expansion in the hepatocytes
  - HBeAg+ most seroconvert to HBeAg- HBV infection, with ↓ HBV DNA (chronic HBV infection) some do not reduce the HBV DNA, and progress to chronic hepatitis B (CHB)
  - Phase 5
    - Occult HBV infection
      - HBsAg-, anti-HBc, +/- anti HBs
      - ALT normal, HBV DNA usually undetectable in serum, but HBV ccDNA in liver



- Give the importance of whether HBsAg is lost before or after the development of cirrhosis.

| HBsAg Loss                                                                               | Risk of HCC |
|------------------------------------------------------------------------------------------|-------------|
| ○ Before development of cirrhosis                                                        | -           |
| ○ After development of cirrhosis                                                         | +           |
| ○ Note                                                                                   |             |
| - HCC develops in HBV infected patients who have been effectively treated, or are HBsAg- |             |



\* the risk of progression from cirrhosis to HCC in persons with chronic hepatitis B infection can be assessed in treated or untreated patients using the PAGE-3 score.

- Give the risk factors for the development of HCC in CBI.

| Host                            | Liver                               | HBV Virus               |
|---------------------------------|-------------------------------------|-------------------------|
| ○ Older                         | - Cirrhosis                         | ▪ ↑ HBV DNA, +/-        |
| ○ Males                         | - Chronic hepatic necroinflammation | ▪ HBsAg+                |
| ○ African race                  |                                     | ▪ HBV genotypes (C > B) |
| ○ Co-infections (e.g., HIV)     |                                     |                         |
| ○ Diabetes / metabolic syndrome |                                     |                         |
| ○ Smoking (current)             |                                     |                         |
| ○ Alcohol (abuse)               |                                     |                         |
| ○ Family history of HCC         |                                     |                         |

➤ Initial laboratory assessment

| Patient                                | 1 <sup>st</sup> Degree Relatives / Sexual Partners |                                           |
|----------------------------------------|----------------------------------------------------|-------------------------------------------|
| ○ HBsAg, anti-HBs                      | HBsAg                                              | } Vaccinate for HBV if tests are negative |
| ○ HBeAg, anti-HBe                      | Anti-HBs                                           |                                           |
| ○ HBV DNA                              | Anti-HBe                                           |                                           |
| ○ ↑ ALT, AST<br>↓ if positive          |                                                    |                                           |
| ○ HBV genotype plus HCV, HDV, HIV, HAV |                                                    |                                           |
| - Abdominal ultrasound (AUS)           |                                                    |                                           |
| - Transient elastography (TE)          |                                                    |                                           |



➤ Treatment

- Give the goals of treatment of HBV.

| Type                      | ↓ Risk                                                                                                                    | Treatment-Associated Serological Changes                                                                        |
|---------------------------|---------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------|
| ○ Acute HBV               | - ↓ acute liver failure (ALF)                                                                                             | ▪ HBeAg+ → HBeAg- / anti-HBe                                                                                    |
| ○ Chronic HBV             | - Progression to cirrhosis, HCC<br>- Extrahepatic complications<br>- Mother-child transmission<br><br>- ↑ quality of life | ▪ HgSAg+ → HBsAg- / anti-HBe<br><br>▪ ↓↓ HBV DNA<br>▪ ↓↓ abnormal ALT / AST<br>▪ ↓ necroinflammation / fibrosis |
| ○ HCC associated with HBV | - Progression<br>- Recurrence<br>- Preparation for HCC treatment                                                          |                                                                                                                 |

Endpoints of Therapy

- The induction of long-term suppression of HBV DNA levels represents the main endpoint of all current treatment strategies (Evidence level I, grade of recommendation 1).
- The induction of HBeAg loss, with or without anti-HBe seroconversion, in HBeAg-positive CHB patients is a valuable endpoint, as it often represents a partial immune control of the chronic HBV infection (Evidence level II-1, grade of recommendation 1).
- A biochemical response defined as ALT normalization should be considered as an additional endpoint, which is achieved in most patients with long-term suppression of HBV replication (Evidence level II-1, grade of recommendation 1).
- HBsAg loss, with or without anti-HBs seroconversion, is an optimal endpoint, as it indicates profound suppression of HBV replication and viral protein expression (Evidence level II-1, grade of recommendation 1).

➤ Indications for treatment of HBV infection

❖ Initial

- HBV DNA - > 2000 IU/mL
- ALT > ULN - (~40 IU/mL)



- Liver biopsy
  - Moderate necroinflammation / fibrosis
  - Biopsy not necessary before Rx if
    - HBV DNA > 20,000 IU/mL
    - Patient refuses biopsy → transient elastography (TE)



Likely severe fibrosis (F3 / cirrhosis)

| TE, kPaa | ALT        |
|----------|------------|
| > 9      | N / ↑      |
| > 12     | ↑ < 5x ULN |

#### Indications for Therapy

- All patients with HBeAg-positive or -negative chronic hepatitis B, defined by HBV DNA > 2,000 IU/mL, ALT > ULN and/or at least moderate liver necroinflammation or fibrosis, should be treated (Evidence level I, grade of recommendation 1).
- Patients with compensated or decompensated cirrhosis need treatment, with any detectable HBV DNA level and regardless of ALT levels (Evidence level I, grade of recommendation 1).
- Patients with HBV DNA > 20,000 IU/mL and ALT > 2x ULN should start treatment regardless of the degree of fibrosis (Evidence level II-2, grade of recommendation 1).
- Patients with HBeAg-positive chronic HBV infection, defined by persistently normal ALT and high HBV DNA levels, may be treated if they are older than 30 years regardless of the severity of liver histological lesions (Evidence level III, grade of recommendation 2).
- Patients with HBeAg-positive or HBeAg-negative chronic HBV infection and family history of HCC or cirrhosis and extrahepatic manifestations can be treated even if typical treatment indications are not fulfilled (Evidence level III, grade of recommendation 2).

❖ Follow up frequency if HBV patient initially not a candidate for treatment

| Serology | HBV DNA, IU/mL | Follow up testing                |            |
|----------|----------------|----------------------------------|------------|
|          |                | ALT                              | HBV DNA/TE |
| HBeAg-   | < 2000         | q 6-12 mon                       | q 2-3 yr   |
|          | ≥ 2000         | q 3 mon for 1 yr<br>then q 6 mon |            |
| HBsAg    | < 1000 IU/mL   | q 1 yr                           | q 3 yr     |
|          | ≥ 1000 IU/mL   | q 6 mon                          | q 2 yr     |



### Monitoring of patients currently not treated

- Patients with HBeAg-positive chronic HBV infection who are younger than 30 years and do not fulfill any of the above treatment indications should be followed at least every 3-6 months (Evidence level II-2, grade of recommendation 1).
- Patients with HBeAg-negative chronic HBV infection and serum HBV DNA < 2,000 IU/mL who do not fulfill any of the above treatment indications should be followed every 6-12 months (Evidence level II-2, grade of recommendation 1).
- Patients with HBeAg-negative chronic HBV infection and serum HBV DNA  $\geq$  2,000 IU/mL who do not fulfill any of the above treatment indications should be followed every 3 months for the first year and every 6 months thereafter (Evidence level III, grade of recommendation 1).

### ➤ Menu of treatment options

- Pegylated interferon (PegIFN) treatment courses of defined duration may produce long-term immunological control (off therapy)
- Nucleot(s)ides analogs (NAs)
  - Adenofovir (ADV)
  - Entecavir (E)
  - Lamivudine (L)
  - Telbivudine (TB)
  - Tenofovir alafenamide (TAF)
  - Tenofovir disoproxil fumarate (FDF)

#### High Barrier to Resistance

- ETV, TAF, TDF
  - Also
    - Can be used in all HBV infected groups
  - But do not usually produce immunological control (i.e., maintenance use of NAs required)

### ➤ Definition of virological and serological responses

|                                  | HBV DNA (IU/mL)                                                                     | PegIFN Therapy                                           |
|----------------------------------|-------------------------------------------------------------------------------------|----------------------------------------------------------|
| ❖ Virological response           |                                                                                     | HBV DNA < 2000 IU/mL at 6 mm and after therapy completed |
| ○ Sustained off-therapy response | < 2000 IU/mL for $\geq$ 12 mon                                                      |                                                          |
| ○ 1° non-response                | $\downarrow$ < one $\log_{10}$ after 3 mon                                          |                                                          |
| ○ Partial response               | $\downarrow$ > one $\log_{10}$ , but detectable HBV DNA after 12 mon                |                                                          |
| ○ Breakthrough                   | $\uparrow$ > one $\log_{10}$ (may occur before ALT, i.e., biochemical breakthrough) |                                                          |
| ○ HBV resistance                 | HBV variants not susceptible to NAs                                                 |                                                          |
| ○ Off-therapy response           | < 2000 IU/mL for 12 mm after completion of therapy                                  |                                                          |



- ❖ Serological response
  - HBeAg+ → HBeAg- / anti-HBe+
  - HBsAg+ → HBsAg- / anti-HBs+
- ❖ Biochemical response
  - Sustained
    - ALT normal (< 40 IU/mL) q 3 mon for 12 - 24 mon post-treatment
- ❖ Histological response
  - Ishak system
    - ↓ necroinflammatory activity ≥ 2 points

### Nucelos(t)ides (NAs)

- HBV non-cirrhotic and compensated cirrhotic treated similarly
- Class effect
  - Lactic acidosis
- Efficacy of NAs with high barrier to resistance

#### MCQ Trick

- Give the risk factors for lactic acidosis is persons treated with NAs.
  - MELD score > 22
  - ↓ eGFR / ↓ Cr<sub>s</sub>
  - Nucleos(t)ides

| HBeAg Status | 5 yr Virological Response | HBeAg Loss  | HBeAg Seroconversion | ALT Normal |
|--------------|---------------------------|-------------|----------------------|------------|
| - HBeAg+     |                           |             |                      |            |
| ▪ ETV        | 99%                       | 53%         | 40                   | 73%        |
| ▪ TDV        | 97%                       | 49%         |                      |            |
| ▪ TAF        | 75% (96 wk)               | 18% (96 wk) |                      |            |
| - HBeAg-     |                           |             |                      |            |
| ▪ ETV        | 98%                       |             |                      |            |
| ▪ TAF        | 90% (96 wk)               |             |                      |            |

Results of main studies for the treatment of chronic hepatitis B at 48 to 52 weeks of nucleos(t)ide analogue (NAs) therapy with antiviral drugs with high barrier to resistance

| NA       | Anti-HBe Seroconversion | HBV DNA < 60 - 80 IU/mL | ALT Normalization |
|----------|-------------------------|-------------------------|-------------------|
| ○ HBeAg+ |                         |                         |                   |
| - ETV    | 67% (90%)*              | 21                      | 68% (78%)         |
| - TDF    | 76 (93%)                | 21                      | 68% (76%)         |
| - TAF    | 64 (94%)                | 10                      | 72% (83%)         |

\* the percentage in brackets refer to HBeAg- patients



- There was no (0%) loss of HBs in the HBeAg- patients and the loss of HBsAg+ patients was only 1 to 3%
- Use high barrier ETV, TAF, TDF
- Do not combine high with low barrier NAs to avoid the development of multidrug resistant strains

| Abbreviations: | Drug                            | Analogue     |
|----------------|---------------------------------|--------------|
| - ETV          | ▪ Entecavir                     | Nucleoside   |
| - TAF          | ▪ Tenofovir alafenamide         | } Nucleotide |
| - TDF          | ▪ Tenofovir disoproxil fumarate |              |

Adapted from: EASL 2017 Clinical Practice Guidelines. J Hepatology 2017; Tables 3 and 4, page 10.

#### NAs for naïve CHB patients

- The long-term administration of a potent NA with high barrier to resistance is the treatment of choice regardless of the severity of liver disease (Evidence level I, grade of recommendation 1).
- The preferred regimens are ETV, TDF and TAF as monotherapies (Evidence level I, grade of recommendation 1).
- LAM, ADV and TBV are not recommended in the treatment of CHB (Evidence level I, grade of recommendation 1).

- Renal dosing
  - eGFR < 50 mL/min      ▪ ETV, TDF
  - < 15 mL/min          ▪ TAF

#### • Give the factors which represent high renal risk.

- Patient
  - Decompensated cirrhosis
  - Transplantation (solid organ)
  - Hypertension
  - Diabetes
 } poorly controlled
- Kidney
  - eGFR < 60 mL/min
  - Proteinuria
  - Glomerulonephritis, active
  - Nephrotoxic drugs
  - TDF
    - Higher nephrotoxic potential to ↓ BMD

Abbreviations: eGFR, estimated glomerular filtration rate; TDF, tenofovir disoproxil fumarate



➤ Suggested monitoring during NA treatment

| Nucleos(t)ide             |                                            | q 3-4 mon x 4 | Subsequently, q 6-12 mon      |
|---------------------------|--------------------------------------------|---------------|-------------------------------|
| For all NAs               | LFT / LE                                   | +             | +                             |
|                           | HBV                                        | +             | +                             |
|                           | HBsAg                                      |               | + (if HBV DNA not detectable) |
| For TDF / high renal risk | eGFR                                       | +             | +*                            |
|                           | PO <sub>4</sub> <sup>2-</sup> <sub>s</sub> | +             | +                             |

\* more frequent monitoring if eGFR < 60 mL/min, or PO<sub>4</sub><sup>2-</sup><sub>s</sub> < 2 mg/dL

Abbreviations: eGFR, estimated glomerular filtration rate; LFT / LE, liver function tests / liver enzymes; PO<sub>4</sub><sup>2-</sup><sub>s</sub>, serum phosphate

Monitoring of patients treated with ETV, TDF or TAF

- All patients treated with NA should be followed with periodical assessments including ALT and serum HBV DNA (Evidence level I, grade of recommendation 1).
- Patients at risk of renal disease treated with any NA and all patients regardless of renal risk treated with TDF should undergo periodical renal monitoring including at least estimated glomerular filtration rate (eGFR) and serum phosphate levels (Evidence level II-2, grade of recommendation 1).
- Patients on TDF at risk of development and/or with underlying renal or bone disease should be considered for a switch to ETV or TAF, depending on previous LAM exposure (Evidence level II-2/I, grade of recommendation 1).

➤ Benefits

- ↓ progression / partial reversal of
    - Cirrhosis
    - Necroinflammation / fibrosis
    - Decompensation / complications
    - HCC risk
  - ↑ survival
  - ↑ delisting for LT
- } Especially with early treatment with NAs

Long-term outcome during NA

- Patients under effective long-term NA therapy should remain under surveillance for HCC (Evidence level II-2, grade of recommendation 1).
- HCC surveillance is mandatory for all patients with cirrhosis as well as those with moderate or high HCC risk scores at the onset of NA therapy (Evidence level II-2, grade of recommendation 1).



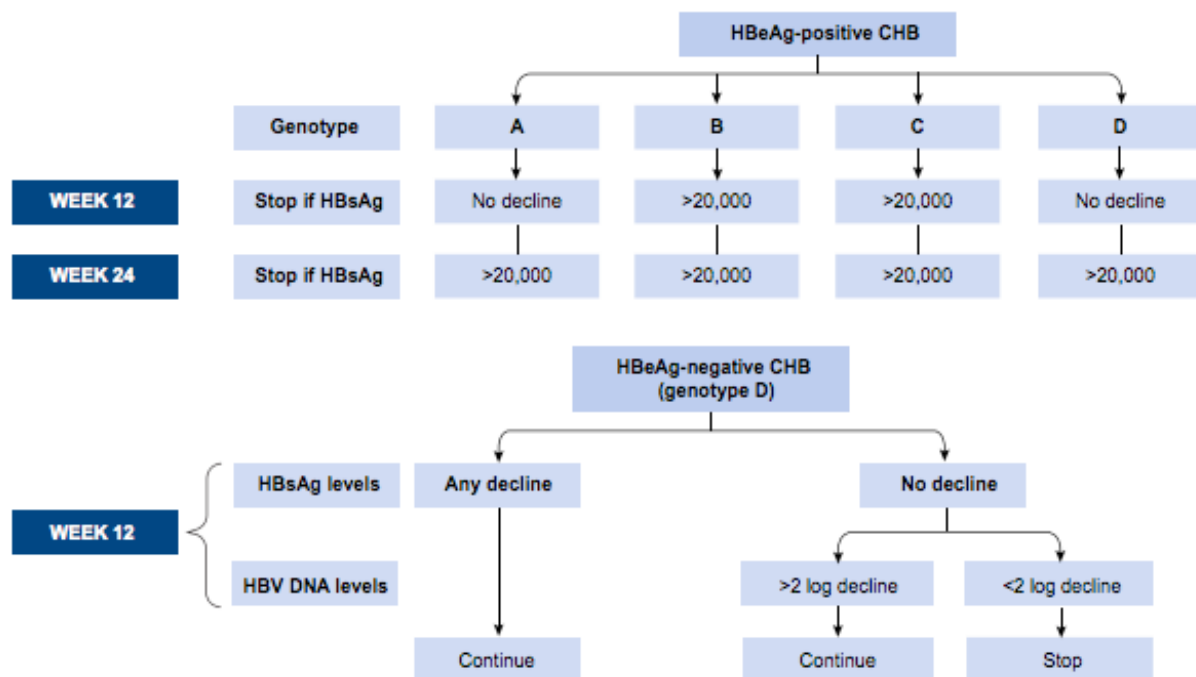


➤ Stopping rules

❖ Nucleos(t)ide analogs

- Long-term maintenance use of nucleos(t)ide analogues (NA)
  - No cirrhosis
    - HBeAg+ chronic hepatitis B (CHB)
      - HBV DNA undetectable on 3 separate occasions 6 mon apart
      - HBeAg seroconversion
    - HBeAg- CHB
      - HBsAg loss
- } > 2-5 yr of virological remission while on NA
- Cirrhosis
    - Do **not** stop NAs

Week 12 and 24 stopping rules for HBeAg-positive and -negative patients treated with PegIFNα. These rules are based upon viral genotype, HBsAg and HBV levels.



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### NA discontinuation

- NAs should be discontinued after confirmed HBsAg loss, with or without anti-HBs seroconversion (Evidence level II-2, grade of recommendation 1).
- NAs can be discontinued in non-cirrhotic HBeAg-positive CHB patients who achieve stable HBeAg seroconversion and undetectable HBV DNA and who complete at least 12 months of consolidation therapy. Close post-NA monitoring is warranted (Evidence level II-2, grade of recommendation 2).
- Discontinuation of NAs in selected non-cirrhotic HBeAg-negative patients who have achieved long-term ( $\geq 3$  years) virological suppression under NA(s) may be considered if close post-NA monitoring can be guaranteed (Evidence level II-2, grade of recommendation 2).

### ➤ Management of failures of first line ETV, TDF and TAF

- Always ensure adherence to recommended drug program
- Partial non-reponse
  - Usually due to use of adenovir (ADV) because of its low potency
  - Switch to ETV, TDF, TAF
- Partial virological response
  - If associated with low barrier LAM, TBV, ADV switch to high barrier ETV, TDF, TAF
  - If associated with use of ETV, TDF, TAF
    - Usually due to very high pretreatment HBV load
    - At 48 wk, if HBV-DNA is lower than baseline, then continue NA for longer
    - If HBV-DNA not falling, then either switch to another NA in the group (ETV, TDF, TAF), or use combined therapy of ETV + TDF or TAF

### Management of patients with NA failure

- Prevention of resistance should rely on the use of first line therapy with high barrier to resistance nucleos(t)ide analogs (NAs) (Evidence level I, grade of recommendation 1).
- Compliance to NA therapy should be checked in all cases of treatment failure (Evidence level II-1, grade of recommendation 1).
- Management of treatment failure should be based on NAs cross-resistance data (Evidence level II-2, grade of recommendation 1).
- Treatment adaptation should be performed as soon as virologic failure under NAs is confirmed (Evidence level II-1, grade of recommendation 1).



## Management of patients who develop NA resistance

| Resistance Pattern        | Recommended Rescue Strategies                                                                                                            |
|---------------------------|------------------------------------------------------------------------------------------------------------------------------------------|
| ○ LAM resistance          | Switch to TDF or TAF                                                                                                                     |
| ○ TBV resistance          | Switch to TDF or TAF                                                                                                                     |
| ○ ETV resistance          | Switch to TDF or TAF                                                                                                                     |
| ○ ADV resistance          | If LAM-naïve: switch to ETV or TDF or TAF<br>If LAM-resistance: switch to TDF or TAF<br>If HBV DNA plateaus: add ETV*** or switch to ETV |
| ○ TDF or TAF resistance** | If LAM-naïve: switch to ETV<br>If LAM-R: add ETV*                                                                                        |
| ○ Multidrug resistance    | Switch to ETV plus TDF or TAF combination                                                                                                |

\* The long-term safety of these combinations is unknown.

\*\* Not seen clinically so far; do genotyping and phenotyping in an expert laboratory to determine the cross-resistance profile.

\*\*\* Especially in patients with ADV resistant mutations (rA181T/V and / or rN236T) and high viral load, the response to TDF (TAF) can be protracted.

Abbreviations: ETV, entecavir; LAM, lamivudine; ADV, adefovir; TAF, tenofovir alafenamide; TBV, telbivudine; TDF, tenofovir disoproxil fumarate

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- Indications for selecting ETV or TAF over TDF\*
  - Age > 60 year
  - Bone disease
    - Chronic steroid use or use of other medications that worsen bone density
    - History of fragility fracture
    - Osteoporosis
  - Renal alteration\*\*
    - eGFR < 60 mL/min/1.73 m<sup>2</sup>
    - Albuminuria > 30 mg or moderate dipstick proteinuria
    - Low phosphate (< 2.5 mg/dL)
    - Hemodialysis

\* TAF should be preferred to ETV in patients with previous exposure to nucleoside analogues.

\*\* ETV dose needs to be adjusted if eGFR < 50 mL/min; no dose adjustment of

TAF is required in adults or adolescents (aged at least 12 years and of at least 35 kg body weight) with estimated creatinine clearance (CrCl) ≥ 15 mL/min or in patients with CrCl 15 mL/min who are receiving haemodialysis.

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- Virological breakthrough
  - Use “treatment adaptation” to overcome HBV drug resistance
  - Refer to published tables of cross-resistance to choose combinations of NAs such as ETV plus TDF
- Special considerations
  - Treatment of patients with **decompensated cirrhosis**
    - Patients with decompensated cirrhosis should be immediately treated with a NA with high barrier to resistance, irrespective of the level of HBV replication, and should be assessed for liver transplantation (Evidence level II-1, grade of recommendation 1).
    - PegIFN $\alpha$  is contraindicated in patients with decompensated cirrhosis (Evidence level II-1, grade of recommendation 1).
    - Patients should be closely monitored for tolerability of the drugs and the development of rare side effects like lactic acidosis or kidney dysfunction (Evidence level II-2, grade of recommendation 1).
  - Prevention of HBV **recurrence after liver transplantation**
    - All patients on the transplant waiting list with HBV related liver disease should be treated with NA (Evidence level II, grade of recommendation 1).
    - Combination of hepatitis B immunoglobulin (HBIG) and a potent NA is recommended after liver transplantation for the prevention of HBV recurrence (Evidence level II-1, grade of recommendation 1).
    - Patients with a low risk of recurrence can discontinue HBIG but need continued monophylaxis with a potent NA (Evidence level II-1, grade of recommendation 2).
    - HBsAg-negative patients receiving livers from donors with evidence of past HBV infection (anti-HBc positive) are at risk of HBV recurrence and should receive antiviral prophylaxis with a NA (Evidence level II-2, grade of recommendation 1).
  - HIV co-infected patients
    - All HIV-positive patients with HBV co-infection should start antiretroviral therapy (ART) irrespective of CD4 cell count (Evidence level II-2, grade of recommendation 1).
    - HIV-HBV co-infected patients should be treated with a TDF- or TAF-based ART regimen (Evidence level I for TDF, II-1 for TAF, grade of recommendation 1).
  - HDV co-infected patients
    - PegIFN $\alpha$  for at least 48 weeks is the current treatment of choice in HDV-HBV co-infected patients with compensated liver disease (Evidence level I, grade of recommendation 1).
    - In HDV-HBV co-infected patients with ongoing HBV DNA replication, NA therapy should be considered (Evidence level II-2, grade of recommendation 1).
    - PegIFN $\alpha$  treatment can be continued until week 48 irrespective of on-treatment response pattern if well tolerated (Evidence level II-2, grade of recommendation 2).



- HCV co-infected patients
  - Treatment of HCV with direct-acting antivirals (DAAs) may cause reactivation of HBV. Patients fulfilling the standard criteria for HBV treatment should receive NA treatment (Evidence level II, grade of recommendation 1).
  - HBsAg-positive patients undergoing DAA therapy should be considered for concomitant NA prophylaxis until week 12 post DAA, and monitored closely (Evidence level II-2, grade of recommendation 2).
  - HBsAg-negative, anti-HBc positive patients undergoing DAA should be monitored and tested for HBV reactivation in case of ALT elevation (Evidence level II, grade of recommendation 1).
- Acute hepatitis B
  - More than 95% of adults with acute HBV hepatitis do not require specific treatment, because they will fully recover spontaneously (Evidence level II-2, grade of recommendation 1).
  - Only patients with severe acute hepatitis B, characterized by coagulopathy or protracted course, should be treated with NA and considered for liver transplantation (Evidence level II-2, grade of recommendation 1).
- Children
  - In children, the course of the disease is generally mild, and most of the children do not meet standard treatment indications. Thus, treatment should be considered with caution (Evidence level II-3, grade of recommendation 1).
  - In children or adolescents who meet treatment criteria, ETV, TDF, TAF, and PegIFN $\alpha$  can be used in this population (Evidence level II-2, grade of recommendation 2).
- Healthcare workers
  - HBV infection alone should not disqualify infected persons from the practice or study of surgery, dentistry, medicine, or allied health fields (Evidence level III, grade of recommendation 1).
  - Healthcare workers performing exposure prone procedures with serum HBV DNA > 200 IU/mL may be treated with NA to reduce transmission risk (Evidence level II-2, grade of recommendation 2).
- Pregnancy
  - Screening for HBsAg in the first trimester of pregnancy is strongly recommended (Evidence level I, grade of recommendation 1).
  - In a woman of childbearing age without advanced fibrosis who plans a pregnancy in the near future, it may be prudent to delay therapy until the child is born (Evidence level II-2, grade of recommendation 2).
  - Pregnant women with CHB and advanced fibrosis or cirrhosis, therapy with TDF is recommended (Evidence level II-2, grade of recommendation 1).
  - In pregnant women already on NA therapy, TDF should be continued while ETV or other NA should be switched to TDF (Evidence level II-2, grade of recommendation 1).
  - In all pregnant women with high HBV DNA levels (> 200,000 IU/mL) or HBsAg levels > 4 log<sub>10</sub> IU/mL, antiviral prophylaxis with TDF should start at week 24–28 of gestation and continue for up to 12 weeks after delivery (Evidence level I, grade of recommendation 1).



- Breastfeeding is not contraindicated in HBsAg-positive untreated women or on TDF-based treatment or prophylaxis (Evidence level III, grade of recommendation 2).
- Patients undergoing immunosuppressive therapy or chemotherapy
  - All candidates for chemotherapy and immunosuppressive therapy should be tested for HBV markers prior to immunosuppression (Evidence level I, grade of recommendation 1).
  - All HBsAg-positive patients should receive ETV or TDF or TAF as treatment or prophylaxis (Evidence level II-2, grade of recommendation 1).
  - HBsAg-negative, anti-HBc positive subjects should receive anti-HBV prophylaxis if they are at high risk of HBV reactivation (Evidence level II-2, grade of recommendation 1).
- Dialysis and renal transplant patients
  - All dialysis and renal transplant recipients should be screened for HBV markers (Evidence level II-2, grade of recommendation 1).
  - HBsAg-positive dialysis patients who require treatment should receive ETV or TAF (Evidence level II-2, grade of recommendation 1).
  - All HBsAg-positive renal transplant recipients should receive ETV or TAF as prophylaxis or treatment (Evidence level II-2, grade of recommendation 1).
  - HBsAg-negative, anti-HBc positive subjects should be monitored for HBV infection after renal transplantation (Evidence level III, grade of recommendation 1).
- Extrahepatic manifestations
  - Patients with replicative HBV infection and extrahepatic manifestations should receive antiviral treatment with NA (Evidence level II-2, grade of recommendation 1).
  - PegIFN $\alpha$  should not be administered in patients with immune-related extrahepatic manifestations (Evidence level III, grade of recommendation 1).

### **PegIFN $\alpha$ (Interferon) Monotherapy**

- PegIFN monotherapy for CHB patients
  - PegIFN $\alpha$  can be considered as an initial treatment option for patients with mild to moderate HBeAg-positive or -negative CHB (Evidence level I, grade of recommendation 2).
    - Cirrhosis, compensated (no portal hypertension)
      - Do not give Peg-IFN in decompensated cirrhosis
      - Do not give Peg-IFN plus telbivudine → ↑ risk of neuropathy
    - Decompensated cirrhosis
      - ETV or TDF, but **no** PegIFN $\alpha$
      - Refer for liver transplantation (LT)
  - The standard duration of PegIFN $\alpha$  therapy is 48 weeks (Evidence level I, grade of recommendation 1).
  - The extension of the duration of PegIFN $\alpha$  therapy beyond week 48 may be beneficial in selected HBeAg-negative CHB patients (Evidence level II-1, grade of recommendation 2).



## ❖ Off-treatment predictors

- Give the pretreatment (**no** treatment) predictors of response to PegIFN.

| Predictors                                                                                                                                                                                                                                                                 | HBeAg+ | HBeAg- |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------|--------|
| ○ Low HBV load                                                                                                                                                                                                                                                             | +      | +      |
| ○ ↑ AST 2 – 5x ULN                                                                                                                                                                                                                                                         | +      | +      |
| ○ HBV genotype                                                                                                                                                                                                                                                             | A,B    | B,C    |
| ○ ↑ histology activity scores                                                                                                                                                                                                                                              | +      |        |
| ○ Young females                                                                                                                                                                                                                                                            |        | +      |
| ○ Combination therapy for CHB                                                                                                                                                                                                                                              |        |        |
| – De novo combination therapy with two NAs with high barrier to resistance (ETV, TDF, TAF) is <b>not</b> recommended (Evidence level I, grade of recommendation 1).                                                                                                        |        |        |
| – In treatment-adherent patients with incomplete suppression of HBV replication reaching a plateau during either ETV or TDF / TAF long-term therapy, a switch to the other drug or combining both drugs may be considered (Evidence level III, grade of recommendation 2). |        |        |
| ○ NA plus PegIFNα                                                                                                                                                                                                                                                          |        |        |
| – De novo combination of NA and PegIFNα is not recommended (Evidence level I, grade of recommendation 1).                                                                                                                                                                  |        |        |
| – In treatment naïve HBeAg-positive patients, short term pretreatment with a NA before PegIFNα is not recommended (Evidence level II, grade of recommendation 1).                                                                                                          |        |        |
| – In long-term NA suppressed CHB patients, adding PegIFNα or switching to PegIFNα is not recommended (Evidence level II, grade of recommendation 1).                                                                                                                       |        |        |

## ❖ On-treatment predictors of response to PegIFN

- Predictors of PegIFNα response and stopping rules
  - In HBeAg-positive CHB patients, HBsAg levels > 20,000 IU/mL for genotype B and C, or no decline of HBsAg levels for genotype A and D, at 12 weeks of PegIFNα therapy are associated with a very low probability of subsequent HBeAg seroconversion and can be used as PegIFNα stopping rules (Evidence level II-2, grade of recommendation 2).
  - In HBeAg-positive CHB patients with genotype A-D, HBsAg levels > 20,000 IU/mL at 24 weeks of PegIFNα therapy are associated with a very low probability of subsequent HBeAg seroconversion and can be used as PegIFNα stopping rules (Evidence level II-2, grade of recommendation 2).
  - In HBeAg-negative CHB patients with genotype D, a combination of no decrease in HBsAg levels and < 2 log<sub>10</sub> IU/mL reduction in serum HBV DNA levels at 12 weeks of PegIFNα therapy predicts no response and should be used as PegIFNα stopping rules (Evidence level II-2, grade of recommendation 1).
- HBeAg+
  - HBsAg < 1500 IU/mL
  - HBsAg > 20,000 IU/mL or genotype B, C  
A, D
  - No decline

} Low predictive value for future HBeAg seroconversion



- HBeAg-
  - $< 2 \log_{10}$  IU/mL ↓ HBV after 12 wk PegIFN $\alpha$ , plus
  - No HBsAg levels in genotype A patients

} Low predictive value for response to PegIFN $\alpha$

❖ On-treatment predictors of sustained viral response (SVR) to PegIFN

- HBeAg-, genotype A, B, or C
  - $\geq 10\%$  ↓ HBsAg from baseline to 12 wk → 46% probability of SVR

Long-term outcome after PegIFN $\alpha$

- Patients with sustained responses after PegIFN $\alpha$  therapy and high baseline HCC risk should remain under surveillance for HCC even if they achieve HBsAg loss (Evidence level III, grade of recommendation 1).

➤ Benefits of sustained off-treatment response to Peg-IFN $\alpha$  therapy

- ↓ necroinflammation / fibrosis
- ↓ risk of HCC (especially in Asia with sustained off-treatment response +/- compensated cirrhosis)
- ↑ loss of HBsAg (~50% in 5 yr)
- ↑ survival

Results of Main Studies for the Treatment of Chronic Hepatitis B at 48 to 52 weeks of Pegylated Interferon (IFN) Therapy

|        | Anti-HBe<br>Seroconversion | HBV DNA<br>( $< 60 - 80$ IU/mL) | ALT Normalization | HBsAg Loss |
|--------|----------------------------|---------------------------------|-------------------|------------|
| HBeAg+ | 29 - 32%                   | 7 - 14% (19%)*                  | 32 - 41% (59%     | 3 - 7% (4% |

\* the percentages in brackets refer to HbeAg- patients

- The ranges of results refer to pegylated IFN-2 $\alpha$  and PegIFN-2b

➤ Suggested monitoring during and after interferon treatment

|                |          | q 3 - 4 mon | Post-treatment<br>Subsequently, q 6 - 12 mon, Long-term |
|----------------|----------|-------------|---------------------------------------------------------|
| ○ All patients | CBC      | +           |                                                         |
|                | ALT      | +           |                                                         |
|                | TSH      | +           |                                                         |
| ○ HBsAg+       | HBV DNA  | +           |                                                         |
|                | HBsAg    | +           |                                                         |
| ○ HBeAg-       | HBeAg    | +           | +                                                       |
|                | Anti-HBe | +           | +                                                       |
|                | HBsAg    |             | +                                                       |





- Give the reasons why HBV patients treated with PegIFN $\alpha$  must have long-term monitoring, even when PegIFN is stopped.
  - Risk of
    - HBeAg- chronic hepatitis B
    - HBeAg seroconversion (to HBeAg+)

#### Monitoring of patients treated with PegIFN $\alpha$

- All CHB patients treated with PegIFN $\alpha$  should be followed with periodical assessments of at least full blood count, ALT, TSH, serum HBV DNA and HBsAg levels (Evidence level I/II-2, grade of recommendation 1).
- HBeAg-positive CHB patients treated with PegIFN $\alpha$  should be also followed with periodical assessments of HBeAg and anti-HBe (Evidence level I, grade of recommendation 1).
- CHB patients with virological response after PegIFN $\alpha$  therapy should remain under long-term follow-up because of the risk of relapse (Evidence level II-2, grade of recommendation 1).

#### ➤ Special treatment groups

##### ❖ Liver transplantation (LT)

- LT candidates with HBV
  - Treatment with NA pre-LT
  - Some will improve enough to delist for LT
- NA plus HBIG → ↓ graft infection with HBV to < 5%
- EBV prophylaxis may be given without HBIG to prevent post-LT recurrence of HBV
- Continue NAs long-term if ↑ risk of post-LT HBV recurrence
  - HBeAg+
  - HBV DNA positive at time of LT
  - Co-infection HDV, HIV
  - Hepatocellular cancer (HCC)
- Give the reason for ↑ risk of nephrotoxicity in post-LT HBV patients on calcineurin inhibitors (CNIs).
  - NAs may have nephrotoxicity, which may be more toxic when CNIs are also used



## Treatment of Chronic Hepatitis B Virus (HBV) Infection: AGAI / EASL Guidelines

Abbreviations: AGAI, American Gastrointestinal Association Institute; EASL, European Association for the Liver

EASL. J Hepatology 2012; 57: 167-85; Martin P, et al. Clin Gastroenterol Hepatol 2015; 13: 2071-87; Reddy RR, et al. Gastroenterology 2015; 148: 215-19; and Perrillo RP, et al. Gastroenterology 2015; 148: 221-44; Nguyen LH, et al. Clin Gastroenterol Hepatol 2014;12:1262-1266; Brahmania M, et al. Lancet Infect Dis. 2016;16(2):e10-21.

### ➤ Chronic HBV classification (historical)

#### I HBeAg+ chronic infection

- HBeAg+, High HBV DNA, normal ALT
  - Rate of spontaneous loss of HBeAg is low, **highly contagious**

#### II HBeAg+ chronic hepatitis

- HBeAg+, high HBV DNA, (↑ ALT (moderate to severe liver inflammation))
  - Most achieve HBeAg seroconversion and HBV DNA suppression

#### III HBeAg-chronic infection

- HBeAg-, HBV DNA < 2000 (can be 200 – 20000), normal ALT
  - 1-3% spontaneous seroconvert / yr
  - Low risk of cirrhosis / HCC in this phase

#### IV HBeAg-chronic hepatitis

- HBeAg-, HBV DNA > 2000 (lower than e+ pts), ↑ ALT
  - Low rate of spontaneous remission

#### V HBsAg-phase

- HBsAg-, HBcAg+, +/- HBsAb
  - If detected HBsAg before cirrhosis, minimal risk of cirrhosis, HCC
  - If cirrhosis before loss of HBsAg remain at risk, continue surveillance
  - Immunosuppression can lead to reactivation

### ➤ Background

- 240 million chronic HBsAg carriers worldwide
- Enveloped DNA virus
- Replicates and assembles exclusively in hepatocytes within the host
- 5-yr cumulative incidence of cirrhosis 8 – 20% in untreated chronic hepatitis B (CHB)
- 5-yr cumulative risk of hepatic decompensation is 20% among cirrhotic
- Annual risk of hepatocellular cancer (HCC) is 2-5%
- Assessment
  - HBV infection
    - Severity, histological changes (necroinflammation, fibrosis)
    - Exclude other causes of chronic liver disease



➤ Causes / associations

- Patient
  - Older age
  - Male sex
  - African origin
  - EtOH abuse
  - Smoker
  - Family history
- Liver
  - Cirrhosis
  - Chronic hepatic necroinflammation
- Comorbidities
  - DM
- Virus
  - HBV DNA
  - HBsAg level
  - HBV genotype C > B

➤ Goal of treatment

- To improve survival and QoL by preventing disease progression (cirrhosis) and HCC
- To prevent mother to child transmission, hepatitis B reactivation
- In HBV-induced HCC, goal is to suppress HBV replication, then to prevent HCC recurrence once curative therapy completed
- In acute HBV, prevent risk of acute or subacute liver failure
- Long-term suppression of HBV replication is main endpoint, HBs loss is optimal endpoint

➤ Indication for treatment

- DNA > 2000 IU/mL, ↑ ALT and/or moderate histological lesions
- All cirrhotic patients with detectable HBV DNA
- Prevention of mother to child transmission
- In patients requiring immunosuppression or chemotherapy
- Long-term potent nucleos(t) analogue with high barrier to resistance represents the treatment of choice

\*Prevention ex: vaccinations are not discussed

- HBeAg-positive or HBeAg-negative
  - Objectives of treatment
    - HBsAg- off therapy sustained virological and biochemical response
    - HBsAg+ on therapy undetectable HBV DNA



| ALT                                  | HBV DNA                              | Monitor ALT                                    | Histologically                     | Treatment                                                            |
|--------------------------------------|--------------------------------------|------------------------------------------------|------------------------------------|----------------------------------------------------------------------|
| Normal (ULN: M, 30 IU/L; F, 19 IU/L) | < 2000 IU/mL<br>Virological response | q 3 mon x 4,<br>then q 6-12                    | Significant disease                | None or yes                                                          |
| ○ Normal                             | ≥ 2000 IU/mL                         | HBeAg-<br>HBeAg+<br>(unless liver biopsy done) | Significant disease or TE abnormal | Entecavir, tenofovir or pegIFN $\alpha$ -2a, especially age 35-40 yr |
| ○ ↑                                  | > 2000 IU/mL                         |                                                |                                    | Entecavir, tenofovir, or pegIFN $\alpha$ -2a                         |

➤ Terms

- Breakthrough
  - Biochemical ↑ ALT > ULN after ALT become normal on therapy
  - Viral ↑ HBV DNA by > 1 log 10 IU/mL above nadir after having virologic response while on therapy

➤ Initial Assessment of patient with chronic HBV infection

- Physical exam, body weight (Les, LFT), abdominal ultrasound, FibroScan
- HBeAg, anti-HBe
- HBV DNA
- HBsAg (particularly in HBeAg – pts)
- HBV genotype not necessary initially, but may be helpful in patients being treated with INF- $\alpha$  for response to Rx
- Co-morbidities, including co-infection (HDV, HCV, HIV)
- HAV, vaccinate if anti-HAV negative

➤ Endpoint of therapy

- Induction of long-term suppression of HBV DNA (1, I)
  - Main cornerstone of treatment, shown to eliminate necroinflammation and progression to fibrosis.
  - No recommendation on level, but lower the better
- Induction of HBeAg loss (1, II-1)
  - Indicated at least partial immune control and often leads to low replication phase endpoint less reliable
  - As such, continuing therapy until HBsAg loss has become alternative strategy
- ALT normalization (1, II-1)
  - Suppression of HBV should normalize ALT level, it does not then elevation may be due to other underlying disease e.g., EtOH, NASH
- HBsAg loss (1, II-1)
  - Optimal endpoint, but rarely achieved
  - HCC may still develop after HBsAg loss (annual risk 0.55%)



## ➤ Treatment

### ❖ Indication

- HBeAg+ / -CHB (HBV DNA > 2000, ALT > ULN) and / or moderate liver necroinflammation or fibrosis (1, I) (need biopsy)
- Cirrhosis (1, I)
- HBV DNA > 20,000 and ALT > 2x ULN (1, II-2) (don't need biopsy, can use non-invasive test)
- HBeAg+ / - CHB and family history of HCC / cirrhosis / extrahepatic manifestations \*2, III)

Abbreviations: CBC, complete blood count; CHB, chronic hepatitis B; eGFR, estimated glomerular filtration rate; HCC, hepatocellular cancer; OP, osteoporosis; ULN, upper limit of normal

### ❖ Strategies

- Options
  - Nucleos(t)ide analogue
  - IFN- $\alpha$  (pegylated)
- Nucleos(t)ide analogs (NAs) approved in Canada include
  - High barrier to resistance entecavir (ETV), tenofovir (TDF – tenofovir disoproxil fumarate; TAF – tenofovir alafenamide)
    - Treatment of choice regardless of liver disease severity (1, I)
    - Preferred regimens are entecavir and tenofovir as monotherapy (1, I)
    - Main advantage of high barrier to resistance is its predictable high long-term antiviral efficacy leading to undetectable HBV DNA levels in the majority of complaint patients as well as its safety profile (uncertainties regarding kidney function and bone disease, does adjust according to eGFR)
    - Can be used in any HBV infected patient, and only option for several subgroups
  - Low barrier to resistance (lamivudine, adefovir, telbivudine)
    - Not recommended in treatment of CHB (1, I)
- Patients on TDF at risk of developing renal or bone disease should be considered for a switch to ETV or TAF, depending on previous LAM exposure (1, II-2)
- ETV / TAF better than TDF if
  - Age > 60
  - Bone disease (steroid use, OP, fragility #'s)
  - Renal disease (eGFR < 60, albuminuria > 30 mg / 24 hr / moderate dipstick, low phosphate hemodialysis)
- PegIFN- $\alpha$  approach is to induce long-term immunological control with a finite duration treatment
- No good evidence with regards to combination therapy yet! (Two studies that showed higher complete HBV DNA suppression, but on-treatment HBV DNA levels, serologic, and clinical difference not strong enough to recommend.)



❖ Definition of response

- Virological response
  - Response = undetectable HBV DNA
  - Primary non-response =  $< 1$  log 10 decrease in HBV DNA by 3 mon
  - Partial response =  $> 1$  log decrease, but detectable HBV DNA by 1 yr
  - In patients who discontinue NA, sustained off-therapy response is HBV DNA  $< 2000$  for at least 1 yr after discontinuing therapy
- Serological response
  - For HBeAg
    - HBeAg loss and HbeAg seroconversion
  - For HBsAg
    - HBsAg loss and HBsAg seroconversion
- Biochemical response
  - Normalization of ALT
    - Because ALT fluctuates, need ALT at least q 3 mon for 1 yr post treatment
    - Transient  $\uparrow$  ALT may occur before long-term biochemical remission, in these patient's follow-up ALT's should be done x 2 years from elevation
- Histological response
  - $\downarrow$  necroinflammation activity by  $\geq 2$  points in histologic activity index on Ishak system
- Response
  - High resistance NA's (Tenofovir and Entecavir) are very effective
    - $> 90\%$  virological response
    - 70-85% biochemical response
    - $\sim 50\%$  loss of HBeAg  $\sim 20\%$  seroconvert
    - HBsAg loss and seroconversion is low (0-3%)
  - \*%'s vary between drugs

❖ Monitoring of patients currently not treated

- HBeAg+ CHB  $< 30$  yr, who do not fulfill any of the above indications should be followed every 3-6 mon (1, II-2)
  - ALT q 3 mon, HBV DNA q 6-12 mon, and FibroScan q 12 mon
- HBeAg-CHB with HBV DNA  $< 2000$  who do not fulfill any of the above indications should be followed every 6-12 mon (1, II-2)
  - ALT q 6-12 mon, HBV DNA / FibroScan q 2-3 yr (HBsAg  $< 1000$  then 12 and 3,  $> 1000$  – 6 and 2)
- HBeAg-CHB with HBV  $> 2000$  who do not fulfill any of the above indications should be followed every 3 x 1 yr and then q 6 mon thereafter (1, III)
  - ALT q 3 mon x 1 yr then q 6 mon. HBV DNA / FibroScan q 12 mon x 3 yr

❖ Monitoring of patients treat with ETV, TDF, TAF (entacavir, tenofovir disoproxil fumarate, tenofovir alafenamide)

- Periodic ALT, HBV DNA (1, I) (from previous q 3 yr, then q 6-12 mon)
- Baseline CBC, liver and kidney function (q 3 mon x 1 yr, then q 6-12 mon)
- Baseline CBC, liver and kidney function (q 3 mon x 1 yr, then q 6 mon)
  - ETV and TDF dose adjustment with eGFR  $< 50$ , ATF at eGFR  $< 25$



- Patient at risk of renal disease and those treated with TDF periodic renal monitoring with eGFR and phosphate (1, II-2)
- Patients should remain on long-term HCC surveillance (1, I)
  - Use PAGE-B score in Caucasians (or several validated in Asian populations) to see if patients are low risk who may not need to be followed.
- ❖ NA discontinuation
  - HBsAg loss (1, II-2)
  - Non-cirrhotic HBeAg+ CHB with stable HBeAg seroconversion and undetectable HBV DNA (after 6-12 months of consolidation therapy (1, II-2)
  - Non-cirrhotic HBeAg-with longterm (> 3 term) virological suppression if close monitoring post-d/c can be guaranteed
  - Re-treatment criteria have not been established
- ❖ NA failure
  - Main prevention of failure is to use high barrier to resistance first line (1, I)
  - Compliance should be checked (1, II-2)
  - Management should be based in NAs cross-resistance data (1, II-2)
    - For most switch to TDF / TAF, if resistance to them switch to ETV, if multidrug resistant then use combo ETV + TDF or TAF (2, III)
    - Also consider combination therapy in patients with plateau (HBV DNA 69 - 2000) and decompensated cirrhosis.
  - Change treatment as soon as virologic failure under NAs confirmed (1, II-2)
    - Primary non-response, partial virological response, or virological breakthrough
      - Partial virological response may be due to very high pretreatment viral load as opposed to lack of efficacy, as such the treatment should be continued given the rise in rates of virological response over time and low risk of resistance with ETV / TDF / TAF
- Treatment (salvage therapy switch)
- ❖ Drug to which resistance developed
  - When resistance develops to lamivudine, entecavir or telbivudin → switch to tenofovir
  - When resistance develops to adenofovir → switch to tenofovir plus entecavir
- ❖ Special Considerations
  - HBeAg+, ALT N, ↑ HBV DNA
    - < 30, no family history of cirrhosis / HCC → no Rx ALT q 3-6 mon
    - < 30, family history of cirrhosis / HCC → liver biopsy, possibly Rx



- HBeAg-, ALT N, HBV DNA > 2000 < 20,000 IU/mL, no evidence of liver disease
  - ALT q 3 mon, plus
  - HBV DNA 6-12 mon for < 3 yr
  - FibroScan® useful
- HBeAg+ / HbeAg- with ALT > 2x ULN plus HBV DNA > 20,000 IU/mL Rx even without liver biopsy or TE
- HBV DNA plus cirrhosis
  - Compensated consider HBV-Rx
  - Decompensated urgent HBV-Rx (NA(S))
  - Nucleotide (nucleoside) analog
  - Nucleosides
    - Lamivudine
    - Emtricitabine
    - Entevacir
    - Telbivudine
  - Nucleotides
    - Adefovir
    - Tenofovir
  - High barrier to development of resistance
    - Entevavir
    - Tenofovir (first-line monotherapies)
  - PEG-IFN for 48 wk for HBeAg+ with chance of anti-HBc seroconversion and sustained off-therapy response

Abbreviations: NA(S), nucleotide / nucleoside analog; PEG-IFN, peginterferon alfa 2a; TE, transient elastography; ULN, upper limit of normal

- Recurrent HBV after liver transplantation
  - Pre-LT NA with high barrier to resistance
  - Post-LT lamivudine +/- adefovir plus HBIG (hepatitis B immunoglobulin) or entecavir
- HIV plus HBV co-infection
- HCV plus HBV co-infection
  - Treat HCV, monitor HBV DNA and treat reactivation with NA(S)
- Acute HBV hepatitis / reactivation of CHB entecavir or tenofovir for
  - ≥ 3 mon after seroconversion to anti-HBs, or
  - ≥ 12 mon after anti-HBc seroconversion, without loss HBsAg
- Healthcare workers
  - HBsAg-positive plus HBV DNA ≥ 2000 IU/mL
    - Treat with entecavir or tenofovir to ↓ HBV DNA to zero or at least < 2000 IU/mL
    - Monitor for drug compliance





- Pregnancy
  - Do not use IFN- $\alpha$
  - FNA category B
    - Tenofovir
    - Telbivudin
  - FNA category C
    - Adefovir
    - Entecavir
    - Lamivudine
  - CHB with
    - No fibrosis: complete pregnancy, then start anti-HBV Rx
    - With fibrosis / cirrhosis: tenofovir
  - Care of infant: viremic area
    - High HBV DNA
      - Mother takes lamivudine, or telbivudine in T3, then infant receives passive plus active immunization
    - Low HBV DNA
      - IgG, HBV vaccination
- End-stage renal disease (dialysis, ↓ renal transplantation)
  - Seronegative
  - NA with dose adjustments for renal function
- Polyarteritis nodosa, glomerulonephritis, skin associations with HBV infection
  - Corticosteroids
  - Plasmapheresis
  - Entecavir, tenofovir

Note: IFN given for these extrahepatic manifestations of HBV may worsen these immune-mediated conditions.

- Preventive therapy before immunosuppressive therapy or chemotherapy (preventing HBV recurrence [HBV<sub>r</sub>]) (AGAI guidelines)
  - Screen all persons scheduled to have immunosuppression or chemotherapy for HBsAg and anti-HBc, and treat before HBV reactivation (HBV<sub>r</sub>)
    - Seronegative
      - Vaccinate for HBV before immune- / chemotherapy
    - HBsAg+
      - Test for HBV DNA → pre-emptive NA (entecavir or regardless of HBV DA level and for 12 mon after tenofovir) discontinue immune- / chemotherapy



**> 10% risk of HBV**

- HBsAg+ / anti-HBc+ treated with prednisone  $\geq 10 - 20$  mg/d for  $\geq 4$  wk, or doxorubicin, or epirubicin (anthracycline derivatives, with HBV DNA detected)
- ENtecavir or tenofovir for 12 mon after immune- / chemotherapy
- HBsAg+/anti-HBc+, or HBsAg- / anti-HBc+
  - Treated with B-cell depleting agents rituximab or ofatumumab and no HBV DNA detected
    - Monitor ALT and HBV DNA: q 1-3 mon give NA if  $\uparrow$  HBV DNA

**1 to 10% risk of HBV**

- HBsAg+ / anti-HBc+, or
- HBsAg- / anti-HBc+, or
  - Treated with
    - TNF- $\alpha$  inhibitors
    - Cytokine or integrin inhibitors
    - Tyrosine kinase inhibitors
- HBsAg+ / anti-HBc+
  - Steroid  $> 10$  mg/d to  $< 20$  mg/d for  $\geq 4$  wk
- Note:
  - Do not use anti-HBs status to grade anti-viral prophylaxis
- In persons with moderate-high risk of HBV who will be given immune- / chemotherapy, screen for HBsAg / anti-HBc

**IFN- $\alpha$  monotherapy**

- Can be first-line for mild moderate HBeAg +/- CHB (2, I)
- Standard duration is 48 wk (1, I)
- Can extended in selected HbeAg-CHB patients (2, II-1)
- Slightly more effective with respect to HBeAg loss and seroconversion as well as HBsAg loss (but still low)
- Do **not** use in decompensated cirrhosis

**❖ Monitoring of patients treated with PegIFN- $\alpha$** 

- CBC, ALT, TSH q 3 mon (1, II-2)
- HBV DNA, HBsAg in all patients and HBeAg, anti-HBe in HBeAg+ CHB patients at 3, 6, 12 mon and 6, and 12 mon post treatment (1, II-2)
- Sustained virological response is usually associated with remission of liver disease, but need to follow-up long-term due to risk of exacerbation and HBeAg seroconversion (HBeAg+ initial patients) (1, II)
- HBsAg q 12 mon in patients with undetectable HBV DNA
- Anti-HBs patients who loss HBsAg (HBsAg+  $\rightarrow$  HBsAg-)



- ❖ Peg-IFN- $\alpha$  pre-treatment predictors of response
  - ↓ viral load, high ALT (2 – 5 x ULN), HBV genotype A + B
  - HBeAg
    - ↑ ALT, ↓ HBV DNA, younger age, female, genotype B + C
    - Scoring system not validated
- ❖ Peg-IFN- $\alpha$  stop rules
  - In HBeAg+ CHB, HBsAg > 20,000 (genotype B + C), or no ↓ HBsAg levels (genotype A + D) by week
    - 12 stop INF- $\alpha$  (2, II-2)
  - In HBeAg+ CHB with genotype A-D, HBsAg > 20,000 at 24 wk
    - Stop PegIFN (2, II-2)
  - In HBeAg-CHB with genotype D, no ↓ HBsAg and < 2 log ↓ HBV DNA at 12 wk (1, II-2)
- ❖ Safety of PegIFN- $\alpha$ 
  - Flu-like symptoms, myalgia, headache, fatigue, weight loss, depression, hair loss, local infection site reaction
  - Hepatitis flares → contraindicated in decompensated cirrhosis
  - Mild myelosuppression → usually improves with decrease in dose of PegIFN- $\alpha$
- Long-term outcomes after PegIFN- $\alpha$ 
  - ↓ HCC incidence and ↑ overall outcomes including ↑ survival (may even be superior to NA for ↓ HCC incidence)
  - Should remain under surveillance for HCC even if HBsAg loss achieved (1, III)
    - This is because although most patients remain HBsAg negative, and there is no progression of liver disease and liver lesions improve histologically, HCC can still develop particularly in those with pre-existing cirrhosis

### NA plus PegIFN- $\alpha$

- **Not** recommended as initial treatment (1, I)
- IN treatment naïve HBeAg+ short term pretreatment with NA before PegIFN- $\alpha$  is **not** recommended (1, II)
- In long-term NA suppressed CHB, adding or switching to PegIFN- $\alpha$  **not** recommended (1, II)
- ❖ Treatment of patients with decompensated cirrhosis
  - Treatment with AN with high barrier to resistance, and should be assessed for liver transplantation (1, II-1)
    - ETV (1 mg OD not 0.5 like in compensated cirrhotic) or TDF are preferred and safe
    - Can use TAF, but fewer studies in this patient population
    - NA's improve function and survival, transplant free survival
      - Earlier treatment → better outcome
      - Higher MELD / Child-Pugh → worse outcome
      - ↓ MELD / Child-Pugh → high predictor off transplant-free survival



- PegIFN- $\alpha$  is contraindicated (1, II-1)
- Monitor for side effects (lactic acidosis, kidney dysfunction) (1, II-2)
- Long-term HCC surveillance
- ❖ Prevention after liver transplantation
  - Hep B Ig + NA after liver transplant for HBV recurrence prevention (1, II-1)
    - ↓ risk of infection to < 5%
    - Monotherapy with NA can be used, but combination therapy recommended in high risk (HBV DNA+, HBeAg+, HCC, HDV, HIV)
  - Patients with low risk recurrence can stop IHBIG (hepatitis B immunoglobulin), but continue NA (1, II-2)
  - HBsAg-patient receiving donor organ with evidence of past HBV infection should receive life-long NA prophylaxis (1, II-2)
- ❖ HIV co-infection
  - Treat with ART, irrespective of CD4 cell count (1, II-2)
    - Due to risk of fibrosis, cirrhosis, and HCC
  - Treat with Tenofovir (TDF or TAF) + ART (1, II-2)
    - Tenofovir has activity against both HBV and HIV
    - Monitor for side-effects (renal, bone, liver)
- ❖ HDV co-infection
  - PegIFN- $\alpha$  x 48 wk is treatment of choice in patients with compensated liver disease (1, I)
    - x 48 wk irrespective of on-treatment response pattern (2, II-2)
  - Consider NA id ongoing HBV DNA replication (> 2000) (1, II-2)
    - NA is the only option if decompensated liver cirrhosis
- ❖ HCV co-infection
  - Treating HCV with direct-acting antiviral (DAA) may reactivating HBV, so if patients fulfill standard criteria for HBV treatment, then treat with NA (1, II).
  - HBsAg+ patients on DAA should be considered for concomitant NA prophylaxis until week 12 post-DAA and monitored closely (2, II-2).
  - HBsAg, anti-HBc on DAA, treat for HBV re-activation if ALT elevation (1, II).
    - In a study of 103 patients, with HBV plus HCV co-infection none had reactivation
- ❖ Acute Hepatitis B
  - > 95% acute HBV have full spontaneous recovery and don't require treatment (1, II-2)
  - Only treat severe acute HBV
    - Coagulopathy (INR > 1.5)
    - Protracted course (persistent symptoms / marked jaundice > 4 wk)
    - Signs of acute liver failure
  - Treat with NA and consider liver transplantation (1, II-2)
    - Early start of NAs → better prognosis
    - Some old data regarding steroids in acute hepatitis, but not discussed in these guidelines (separate EASL CPG's [Clinical Practice Guidelines])



## ❖ Children

- Usually mild disease, and normally don't meet treatment criteria. Treatment should be considered with caution (1, II-3).
  - Conservative approach is warranted
- If meet criteria for treatment, ETV, TDF, TAF, and PegIFN- $\alpha$  can be used (2, II-2)
  - Studies show safety, improve virological response, but no significant HBeAg loss

## ❖ Healthcare workers

- Can still practice medicine if HBV infected (1, III).
- If performing exposure-prone procedures with DNA > 2000, then treat with NA to ↓ risk of transmission (2, II-2)
  - Centre for disease control (CDC) recommendation is to restart procedure is DNA < 1000

## ❖ Pregnancy

- Screen with HBsAg in first trimester (1, I).
  - If found HBV + during pregnancy, assess risks and benefits (no guidelines)
- In woman without advanced fibrosis who is planning for pregnancy, delay therapy until child is born (2, II-2).
- If pregnant with CHB and advanced fibrosis / cirrhosis → treat with TDF (1, II-2)
- If on other NA → switch to TDF (1, II-2)
  - PegIFN- $\alpha$  contraindicated in pregnant patient
  - Can be used in patients planning for pregnancy as it has a finite course → if not successful or can't then use TDF throughout, even during next pregnancy
- HBV DNA > 200,000 or HBsAg > 4 log prophylaxis with TDF should start at week 24-28 of gestation, and continue up to 12 wk after delivery.
  - Normal prophylaxis is HBIG and vaccination within 12 hr of birth (↓ vertical transmission from > 90% to 10%)
- Breastfeeding is not contraindicated in HBsAg+ untreated women or TFD
  - Based treatment (although it does pass into breast milk, bioavailability is limited)

## ❖ Patients on immunosuppressive therapy or chemotherapy

- Test all for HBV markers prior to chemo / immunosuppressive therapy (1, I).
  - If found HBV + during pregnancy, assess risks and benefits (no guidelines)
- HBsAg+ treat or prophylaxis with ETV / TDF? Or TAF (II-2)
  - Prophylaxis for at least 12 mon (18 mon if rituximab) after cessation of immunosuppressive treatment and discontinue only if underlying disease in remission.
  - Liver function and HBV DNA q 3-6 mon, 12 mon after NA withdrawal (10% reactivation rate)
- HBsAg-, Anti-HBc+ give anti-HBV prophylaxis if high risk for HBV reactivation (1, II-2)
  - High risk reactivation with rituximab

## ❖ Dialysis and renal transplant patients

- Screen for HBV markers (1, II-2)
  - Vaccinate HBV seronegative patients



- HBsAg+ dialysis patients who require treatment should receive ETV (recommended in treatment naïve patients) or ATF (either naïve or previously treated) (1, II-2).
  - Adjust ETV eGFR < 50, ATF eGFR < 50, ATF eGFR < 15
- HBsAg+ renal transplant patient should receive ETV or TAF prophylaxis (1, II-2).
- HBsAg-, anti HBc+ monitor for HBV infection after renal transplantation
  - No treatment (1, III)
  - If seroconversion then treat with ETV
- ❖ Extrahepatic manifestations
  - Treat with NA if HBV DNA+ (1, II-2)
    - Extrahepatic
      - Vasculitis, purpura, PAN, arthralgias, peripheral neuropathy, glomerulonephritis, cryoglobulinemia, rheumatoid factor-positive, elevated CRP / ESR / complement
  - Do not use PegIFN- $\alpha$  (1, III)
    - Can precipitate extrahepatic manifestations
  - Special considerations
    - Corticosteroids
    - Changing to other immune-suppressive drug
- New biomarkers of HBV infection
  - ccDNA is key genomic form for persistent infection
  - Biopsy required, so surrogate biomarkers used (HBsAg)
  - cccDNA levels and transcriptional activity may be important in future treatment concepts to cure HBV infection
  - HBcrAg (HB core-related Ag) may provide additional transcriptional data and be helpful in HBeAg- patients, HCC risk, or NA / PegIFN- $\alpha$  treatment efficacy.
  - HBV RNA may be helpful in predicting viral rebound after discontinuation of NA.
- Future treatment options
  - Many studies ongoing with direct-acting antivirals and immune modulation
- Unresolved issues and unmet needs
  - When to start antiviral therapy in patients with HBeAg-positive chronic HBV infection
  - Stopping rules for HBeAg-negative patients treated with NA
  - Retreatment criteria after NA discontinuation
  - How to accelerate HBsAg decline in long-term NA treated patients?
  - Better baseline or on-treatment predictors of sustained treatment in patients treated with PegIFN- $\alpha$
  - Definition of the residual risk of HCC in patients with finite duration and high cure rates
  - Definition of novel endpoints to define a cure of HBV infection
  - Biomarkers for the cure of infection and for the cure



## HBV INFECTION REACTIVATION DURING IMMUNOSUPPRESSIVE DRUG THERAPY

Reddy RR, et al. AGA Institute Guideline. Gastroenterology 2015; 148: 215-219

Please also see Perrillo RP, et al. Gastroenterology 2015; 148: 221-244.

### ➤ Overview

- Give the rationale for giving HBV prophylactic therapy rather than giving treatment for persons who have regular monitoring of their DNA levels as an early indication of treatment with ↑ HBV DNA representing early HBVr (“on-demand therapy”).
  - The rate of HBVr is lower with prophylactic HBV therapy then with on-demand HBV treatment

- |                                                                                                                                                                                                 |                                  | Risk of HBVr |   |                                    |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------|--------------|---|------------------------------------|
| ○ Immunosuppressant drug: TNF-alpha inhibitor                                                                                                                                                   | - HBsAg+<br>- Anti-HBc+ / HBsAg+ | 40%<br>5%    | } | Fatalities have occurred with HBVr |
| ○ Benefit of HBV anti-viral prophylaxis with entecavir                                                                                                                                          |                                  |              |   |                                    |
| - Relative risk reduction (RRR)                                                                                                                                                                 |                                  |              |   |                                    |
| ▪ HBV reactivation, 87%                                                                                                                                                                         |                                  |              |   |                                    |
| ▪ HBV hepatitis, 84%                                                                                                                                                                            |                                  |              |   |                                    |
| ○ The risk of reactivation of hepatitis B viral (HBVr) infection during immunosuppressive drug therapy depends upon the HBV serology, as well as upon the drugs used for the immunosuppression. |                                  |              |   |                                    |

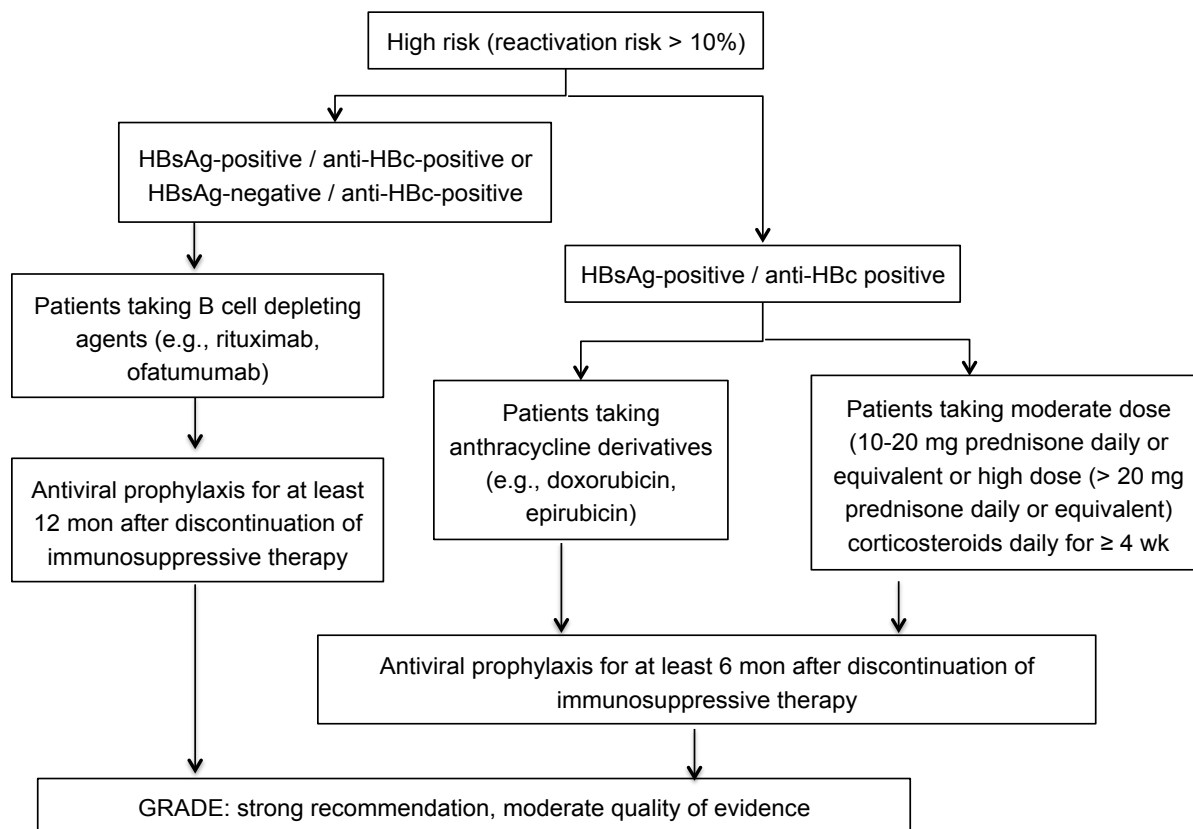
### ❖ High-risk group

| HBV Serology             | Immunosuppressive Drug Used             |                        |
|--------------------------|-----------------------------------------|------------------------|
| ○ HBsAg+ / anti-HBc+, or | Rituximab                               | B-cell depleting drugs |
| ○ HBsAg- / anti-HBc+     | Ofatumumab                              |                        |
| ○ HBsAg+ / anti-HBc+     | Doxorubicin<br>Epirubicin<br>Prednisone | Anthracene derivatives |
| ○ HBV treatment          | Prednison 10-20, or > 20                | ≥ 6 mon                |



## AGA Institute Guidelines on Hepatitis B Reactivation (HBVr)

## Clinical Decision Support Tool

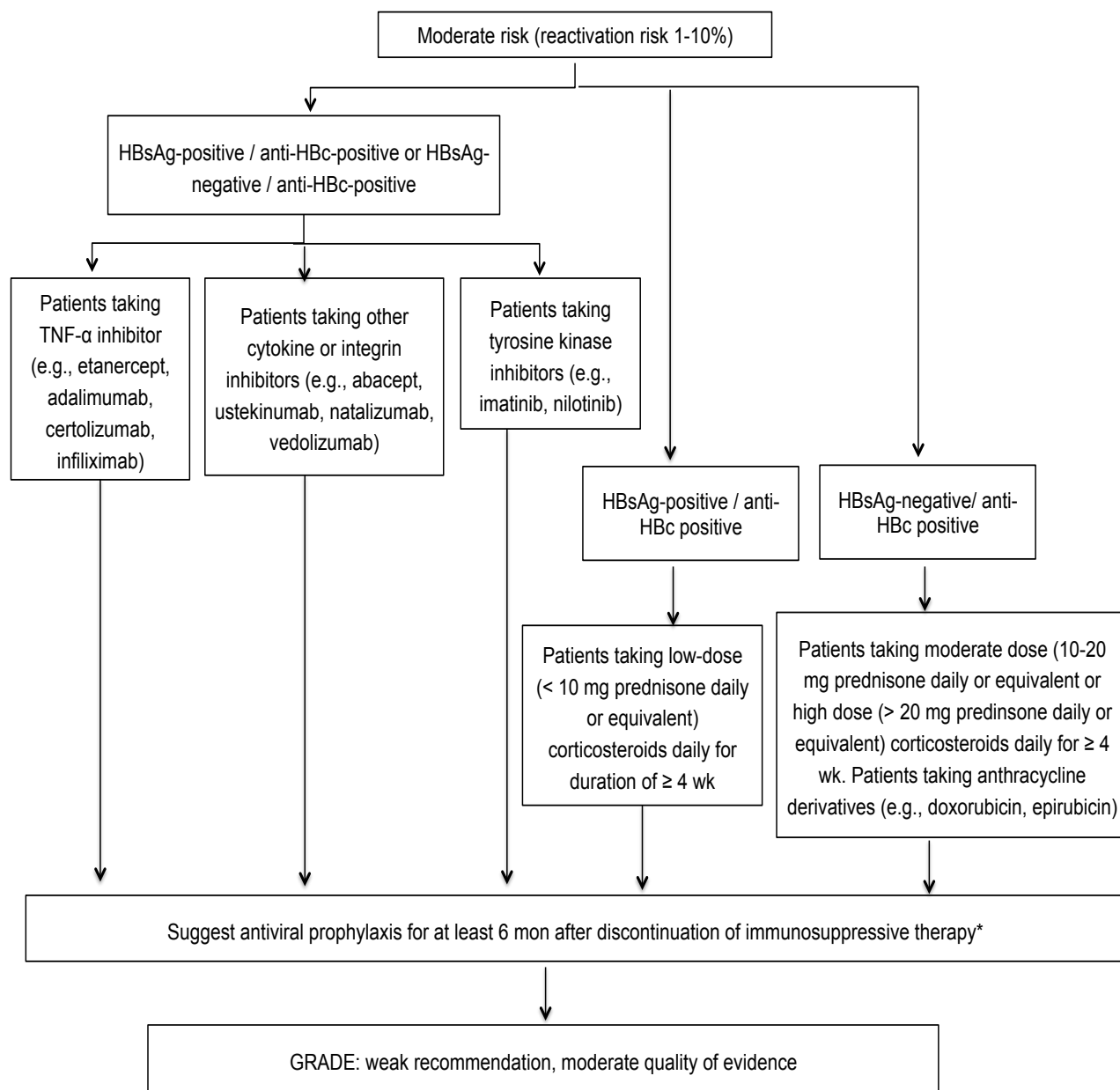


## ❖ Medium-risk HBVr (1% to 10%)

| HBV Serology                                                                                             | Immunosuppressant Used                            |                                           |
|----------------------------------------------------------------------------------------------------------|---------------------------------------------------|-------------------------------------------|
| <ul style="list-style-type: none"> <li>○ HBsAg+ / anti-HBe+, or</li> <li>○ HBsAg- / anti-HBc+</li> </ul> | Infliximab                                        | } Tumour necrosis factor alpha inhibitors |
|                                                                                                          | Adalimumab                                        |                                           |
|                                                                                                          | Certolizumab                                      |                                           |
|                                                                                                          | Etanercept                                        | } Alpha 4 integrin inhibitors             |
|                                                                                                          | Vedolizumab                                       |                                           |
| <ul style="list-style-type: none"> <li>○ HBsAg+ / anti-HBc+</li> </ul>                                   | Natalizumab                                       | } Cytokine inhibitors                     |
|                                                                                                          | Ustekinumab                                       |                                           |
|                                                                                                          | Abatacept                                         | } Tyrosine kinase inhibitors              |
|                                                                                                          | Imatinib                                          |                                           |
|                                                                                                          | Nilotinib                                         |                                           |
| <ul style="list-style-type: none"> <li>○ HBsAg+ / anti-HBc+</li> </ul>                                   | Prednisone                                        | } Anthracycline derivatives               |
|                                                                                                          | < 10 mg/d, for ≥ 4 wk<br>10-20 mg/d, or > 20 mg/d |                                           |
| <ul style="list-style-type: none"> <li>○ HBsAg+ / anti-HBc+</li> </ul>                                   | Doxorubicin                                       | } Anthracycline derivatives               |
|                                                                                                          | Epirubicin                                        |                                           |







\* Patients who place a higher value on avoiding the long-term use of antiviral therapy and cost associated with its use and a lower value on avoiding the small risk of reactivation (particularly in those who are HBsAg-negative), may reasonably select no prophylaxis over antiviral prophylaxis

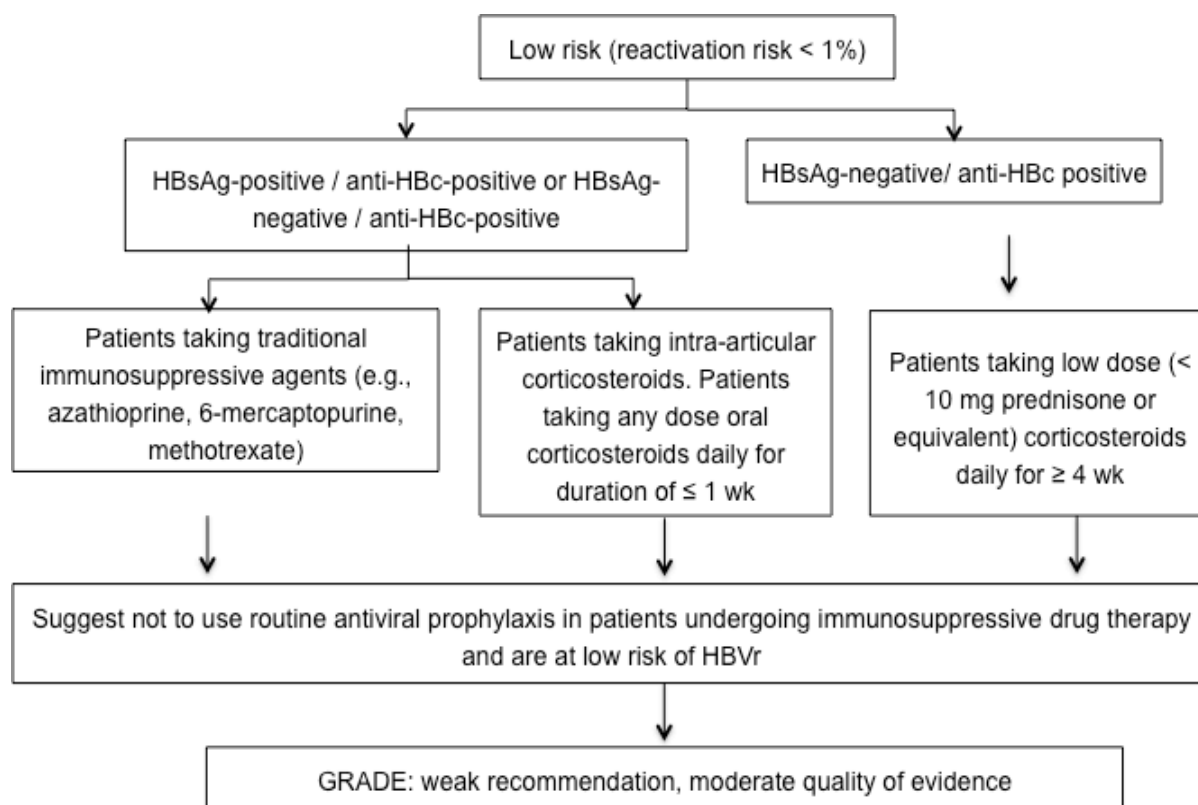


## ❖ Low-risk HBVr (&lt; 1%)

| HBV Serology             | Immunosuppressive Drug                  |
|--------------------------|-----------------------------------------|
| ○ HBsAg+ / anti-HBc+, or | – Azathioprine                          |
| ○ HBsAg- / anti-HBc+     | – 6-mercaptopurine                      |
|                          | – Methotrexate                          |
|                          | – Intraocular                           |
|                          | – Corticosteroids                       |
|                          | – Oral corticosteroids, any dose ≤ 1 wk |

## HBsAg- / anti-HBc+

- Give data to the reason why antiviral treatment is not recommended for prevention of HBVr in low risk groups (risk of HBVr < 1%).



Source: Perrillo RP, et al. Gastroenterology 2015; 148: 221-244



### Aide de Memoire

- The only patients who require 12 mon HBV therapy to prevent HBVr is
  - The B-cell depleting drugs rituximab and ofatumumab in persons who are
    - HBVAg+ / anti-HBc+, or
    - HBsAg- / anti-HBc+
  - Baseline HBV DNA > 2000 IU
- All recommendations apply for HBsAg+ / anti HBc+
- The only recommendations that also apply for HBsAg- / anti-HBc+ serology are for inhibitors of
  - B cell depleting drug
  - TNF- $\alpha$  inhibitors
  - Integrin inhibitors
  - Cytokine inhibitors
  - Tyrosine kinase inhibitor
- HBV therapy to prevent HBVr is not recommended for any of the above serology pattern (HBsAg+ / anti-HBc+ or HBsAg- / anti-HBc+) for
  - Traditional immunosuppressants
    - Azathioprine, 6-MP, methotrexate
  - Corticosteroids
    - Any dose for  $\leq 1$  wk
    - < 10 mg prednisone  $\geq 4$  wk
    - Intraocular prednisones

### MCQ Trick

- Give the role of anti-HBs+ in risk stratification for HBVr.
  - > 66% of patients who are anti-HBc+ also are anti-HBs+
  - Anti-HBs+ provides additional protection against HBVr
  - However, there is "...insufficient evidence to support the use of anti-Hbs titres in making a recommendation regarding prophylaxis"

- Lamivudine is not the first-line drug because of its barrier ( $\uparrow$  risk) to resistance
  - Lamivudine resistance
    - 1 yr, 20%
    - 2 yr, 30%

### ➤ Recommendations

- Perform screening for HBV HBsAg and anti-HBc, followed by a sensitive test for HBV DNA in every person who is to be placed on regimen on immunosuppression, which has a high or medium risk of HBV reactivation.



- Use third generation nucleos(t)ide analogs for patients who are at high or medium risk of HBV reactivation (HBVr) continuing therapy for at least 6 mon after discontinuation of immunosuppressive therapy, except for the B-cell depleting agents for which treatment should be continued for at least 12 mon.
- Do not use
  - HBV DNA monitoring and on-demand treatment
  - HBV treatment for persons at low risk for HBVr
  - Anti-HBV drugs with low barrier to the development of resistance (e.g., lamivudine)
- Do use anti-HBV DNA drugs which high barrier to resistance, e.g., entecavir or tenofovir

AGA Institute <http://www.gastro.org/practice/medical-position-statements/aga-institute-clinical-practice-guideline-development-process>

### SO YOU WANT TO BE A GASTROENTEROLOGIST!

- Give the reason why reactivation of HCV infection (HCVr) is a high or medium-risk cancer in persons who are anti-HBc+ +/- HBsAg+.
  - Using prednisone at a dose  $\geq 10$  mg/d for  $\geq 4$  wk represents a risk for HBVr
    - HBV genome contains a glucocorticosteroid response element (GRE), aka transcriptional regulatory element [TRE] is incorporated into the patient's DNA
    - Corticosteroids
      - Stimulate HBV genome sequence
      - $\downarrow$  cytotoxic T-cell function

### SO YOU WANT TO BE A GASTROENTEROLOGIST!

- Rituximab is mostly used to treat hematologic malignancy, but the gastroenterologist may be consulted if the patient has positive HBV serology (anti-HBc+ +/- HBsAg+).
  - Entecavir or tenofovir need to be started in the patient before the B-cell depleting agent is started, since this class of drugs has a  $> 10\%$  risk of causing HBVr
    - Anti-HBV drugs must be continued for at least 12 mon after the rituximab is discontinued.
- Give the reason why this class of immunocompressants has a high risk of HBVr ( $> 10\%$ ).
  - HBVr may occur up to 12 mon after the B-cell depleting drug has been stopped
  - In patients who are anti-HBc+, the rate of seroreversion is 25 - 45%
  - HBVr may cause acute liver failure, and the need for liver transplantation



| Indication for use of Immunosuppressant Drugs | HBVr | HBV-Hepatitis | Death |
|-----------------------------------------------|------|---------------|-------|
| ○ Lymphoma                                    | 50%  | ~50%          | 3%    |
| ○ Breast cancer                               | ~20% | 60%           |       |
| ○ HCC and TACE*                               | 40%  | ~50%          | 20%   |
| ○ HCC and systemic chemotherapy               | ~35% | ~50%          |       |

Abbreviations: AHR, adjusted hazard ratio; HCC, hepatocellular cancer; TACE, transarterial chemoembolization

\* HBVr may occur several months after TACE has been completed

#### AHR versus local ablation

- Treatment
  - Adriamycin 2.45
  - 2 drugs 4.19
  - 2 drugs plus radiotherapy 10.2
- High level viremia-baseline HBV DNA >  $10^4$  copies (2000 IU/mL)

#### MCQ Trick

- The risk of HBVr using medium-risk immunosuppressants is lower in anti-HBc+ than in HBsAg+
  - Note however that with high-risk immunosuppressants, HBVr is anti-HBc+ = HBsAg+
- The rate of HBVr in anti-HBc+ chemotherapy patients is much less than in serological counterparts given cancer chemotherapy.



## HCV INFECTION

### Treatment of HCV Infection: AASLD / CASL and EASL Guidelines

Abbreviations: AASLD, American Association for the Study of Liver Diseases; Canadian Association for the Study of the Liver; EASL, European Association for the Liver

CASL. Myres RP, et al. Can J Gastroenterol Hepatol 2015; 29: 19-34; and 2012; 26:359-75; EASL. J Hepatol. 2017;66(1):153-194; and AASLD. Ghany MG, et al. Hepatology 2011; 54: 1433-42; and Hepatology 2009; 49: 1335-42; Webster DP, et al. Lancet. 2015 21;385(9973): 1124-35.

#### ➤ Staging

- Liver biopsy and the METAVIR or modified Ishak score system remain the gold standard to diagnose and stage hepatic fibrosis.
  - Less invasive and more reproducible methods are needed to make this diagnosis, and to be able to follow the possible therapeutic-associated benefit of regression of fibrosis.
  - However, < 40% of identified biomarkers were validated for the METAVIR-derived models, despite high predictive performance for fibrosis classification.
- Metabolic phenotyping is an established and powerful tool, providing a window into systemic metabolism through analysis of biological samples by analytical technologies (such as magnetic resonance (NMR) spectroscopy coupled with multivariate data analysis”.
- The enhanced liver fibrosis model (ELF) derived from plasma metabolic phenotypes reflective of chronic hepatitis C-induced fibrosis demonstrated changes in amino-acid and lipid metabolism.
- > 80% of the biomarkers in ELF were validated
  - Amino-acid metabolism
    - Tyrosine, phenylalanine, methionine, citrate, creatine
  - Lipid metabolism
    - VLDL, LDL, phosphatidyl choline
    - N-acetyl- $\alpha$ 1-acid-glycoprotein

Sands CJ, et al. Am J Gastroenterol 2015; 110: 159-169.

#### ➤ Laboratory (screening and diagnosis)

- HCV RNA, genotype and subtype, including IL28B
- Transient elastography (TE; FibroScan®), and biomarkers to assess fibrosis extent
- The HCV genotype and genotype 1 subtype (1a or 1b)
  - Assess prior to treatment initiation and will determine the choice of therapy, among other parameters (A1)
- Systematic testing for HCV resistance prior to treatment is not recommended. (B1).



- Physicians who have easy access to a reliable test assessing HCV resistance to NS5A inhibitors (spanning amino acids 24 to 93)
  - Use these results to guide their decisions
  - The test should be based on population sequencing (reporting resistance associated substitutions (RASs) as “present” or “absent”) or deep sequencing with a cut-off of 15% (only RASs that are present in more than 15% of the sequences generated must be considered) (B1).

Get Genotype (don't need resistance testing...but can get it if available)

#### ➤ Diagnosis

- Anti-HCV antibodies are the first line diagnostic test for HCV infection (A1).
- In the case of suspected acute hepatitis C or in immunocompromised patients, HCV RNA testing should be part of the initial evaluation (A1).
  - May be negative in early HCV or immunosuppressed pts
  - May remain positive following treatment or spontaneous clearance
  - In all positive cases HCV RNA will be detected
- If anti-HCV antibodies are detected, HCV RNA should be determined by a sensitive molecular method (A1).
- Anti-HCV positive, HCV RNA-negative individuals should be retested for HCV RNA 3 months later to confirm definitive clearance (A1).
- HCV core antigen is a surrogate marker of HCV replication and can be used instead of HCV RNA to diagnose acute or chronic infection when HCV RNA assays are not available or not affordable (core antigen assays are slightly less sensitive than HCV RNA assays for detection of viral replication) (A1).
- Reinfection is defined as recurrence >6 months from SVR with different strain (different genotype or distantly related strain on phylogenetic analysis)

ANTI HCV Abx → IF + get HCV RNA (or HCV core Ag)

#### ➤ Screening

- Screening for HCV infection is presently based on the detection of anti-HCV antibodies (A1).
- Whole blood sampled on dried blood spots can be used as an alternative to serum or plasma obtained by venipuncture (A1).
- Rapid diagnostic tests using serum, plasma, fingerstick whole blood or crevicular fluid (saliva) as matrices can be used instead of classical enzyme immunoassays to facilitate anti-HCV antibody screening and improve access to care (A1).
- If anti-HCV antibodies are detected, HCV RNA, or alternatively HCV core antigen if HCV RNA assays are not available or not affordable, should be determined to identify patients with ongoing infection (A1).



➤ Treatment

- Note
  - “Due to the rapidity of advances in this field, recommendations in the present document will be updated regularly as new information emerges and novel agents are approved”.

➤ Goals and End-point

- The goal of therapy is to cure HCV infection to prevent hepatic cirrhosis, decompensation of cirrhosis, HCC, severe extrahepatic manifestations and death (A1).
- The endpoint of therapy is undetectable HCV RNA in blood by a sensitive assay (lower limit of detection  $\leq 15$  IU/mL) 12 weeks (SVR12) and / or 24 weeks (SVR24) after the end of treatment (A1).
- In patients with detectable HCV core antigen prior to therapy, undetectable HCV core antigen 12 weeks (SVR12) and / or 24 weeks (SVR24) after the end of treatment is an alternative endpoint of therapy if HCV RNA assays are not available or not affordable (A1).
- In patients with advanced fibrosis and cirrhosis, HCV eradication reduces the rate of decompensation and will reduce, albeit not abolish, the risk of HCC. In these patients surveillance for HCC should be continued (A1).

Goal is to cure, so confirm with SVR 12 or 24 (HCV RNA or core Ag, if prev +)

➤ Pre-Therapeutic Assessment

- The causal relationship between HCV infection and liver disease should be established (A1).
- The contribution of comorbid conditions to the progression of liver disease must be evaluated and appropriate corrective measures implemented (A1).
  - Hep B, HIV, EtOH, Hepatotoxic meds, autoimmune conditions, others
- Liver disease severity should be assessed prior to therapy. Identify patients with cirrhosis (A1).
  - If cirrhosis then screening with EGD for varices and q6 monthly U/S
- Fibrosis stage can be assessed by non-invasive methods initially, with liver biopsy reserved for cases where there is uncertainty or potential additional aetiologies (A1).
- Cardiac and renal function should be ascertained (A1).

Rule out other causes → assess for fibrosis (fibroscan +/- fibrotest)

➤ Contraindications to Therapy

- NONE
- NS3-4A protease inhibitors (simeprevir, ritonavir, paritaprevir, or grazoprevir) should not be used in Child-Pugh C or decompensated (or previously decompensated) Child-Pugh B due to higher protease inhibitor concentration in these patients





➤ Indications for Treatment

- All treatment-naïve and treatment-experienced patients with compensated or decompensated chronic liver disease due to HCV must be considered for therapy (A1).
  - Treatment should be considered without delay in patients with: (A1)
    - Significant fibrosis or cirrhosis (METAVIR score F2, F3 or F4)
    - Decompensated (Child-Pugh B or C) cirrhosis
    - Clinically significant extra-hepatic manifestations (e.g., symptomatic vasculitis associated with HCV-related mixed cryoglobulinaemia, HCV immune complex-related nephropathy and non-Hodgkin B cell lymphoma)
    - HCV recurrence after liver transplantation
    - Individuals at risk of transmitting HCV (active injection drug users, men who have sex with men with high-risk sexual practices, women of child-bearing age who wish to get pregnant, haemodialysis patients, incarcerated individuals)
  - Patients with decompensated cirrhosis and an indication for liver transplantation with a MELD score  $\geq 18$ -20 should be transplanted first and treated after transplantation. If the waiting time is more than 6 months, these patients can be treated before transplantation (B1).
  - Treatment is not recommended in patients with limited life expectancy due to non-liver-related comorbidities (B2).
- Give a classification of the drugs used in interferon-free regimen for treatment of HCV infection.
    - NS3-4A            protease inhibitors
    - NS5A            inhibitors
    - NS / NT        analogs
    - Non-NS / NT   inhibitors (of the HCV RNA-dependent RNA polymerase)
    - There are first and second generation (2<sup>nd</sup> – gen) protease inhibitors and NS5A inhibitors

Abbreviation: NS, nucleoside; NT, nucleotide

- Indications for treatment
  - All persons with HCV infection, including those with cirrhosis, and extra-hepatic associations

| Agent Class                                                               | Generation              | Compound                                                                       |
|---------------------------------------------------------------------------|-------------------------|--------------------------------------------------------------------------------|
| ○ NS3-4A protease inhibitors                                              | – Ia, first generation  | Telaprevir (TEL)<br>Boceprevir (BOC)<br>Simeprevir (SIM)<br>Paritaprevir (PAR) |
|                                                                           | – Ib, second generation | Grazoprevir (GRA)<br>ACH-2684                                                  |
| ○ Nucleoside / nucleotide analogs                                         | – Nucleotide analog     | Sofosbuvir (SOF)                                                               |
| ○ Non-nucleosides inhibitors of the HCV<br>– RNA-dependent RNA polymerase | –                       | Dasabuvir (DAS)<br>Beclabuvir (BEC)                                            |



| Agent Class       | Generation               | Compound                                                  |
|-------------------|--------------------------|-----------------------------------------------------------|
| ○ NS5A inhibitors | – First generation       | Daclatasvir (DAC)<br>Ledipasvir (LED)<br>Ombitasvir (OMB) |
|                   | – IIb, Second generation | Elbasvir (ELB)                                            |

❖ Ritonavir-boosted paritaprevir, ombitasvir and dasabuvir (Viekira + dasabuvir) – Genotype 4

- Mechanism of action
  - Paritaprevir is an NS3-4A protease inhibitor
  - Ombitasvir is an NS5A inhibitor
  - Dasabuvir is a non-nucleoside inhibitor of HCV RNA-dependent RNA polymerase
- Dose:
  - Two tablets of ritonavir / paritaprevir / ombitasvir (50 mg / 75 mg / 12.5 mg per tablet)
  - Dasabuvir – 250 mg tablets administered twice daily in combination with ritonavir / paritaprevir / ombitasvir in genotype 1 patients.
- AE
  - Fatigue and nausea
- Paritaprevir and ombitasvir fecal elimination, dasabuvir fecal and biliary (min. renal)
- Ritonavir boosted paritaprevir and ombitasvir with or without dasabuvir is not recommended for patients with Child-Pugh B and is contraindicated in patients with Child-Pugh C.
- No dose adjustment for renal failure
- Ritonavir is a strong inhibitor of CYP3A4
  - Contraindicated inhibitors include: alfuzosin, amiodarone, astemizole, terfenadine, cisapride, ergot derivatives, lovastatin, simvastatin, atorvastatin, oral midazolam, triazolam, quetiapine, quinidine, salmeterol, sildenafil when used for pulmonary arterial hypertension.
  - Caution with inducers: carbamazepine, phenytoin, phenobarbital, rifampicin, St John's wort, enzalutamide, and enzyme inhibitors that might increase paritaprevir exposure, e.g., azole antifungals, some macrolide antibiotics.
  - Caution in co-infection with HIV. Atazanavir and darunavir should be taken without ritonavir and other protease inhibitors (Efavirenz, etravirine and nevirapine) are contraindicated

❖ Grazoprevir and elbasvir (Zepatier) – Genotype 1 and 4

- MOA:
  - Grazoprevir is an NS3 / 4A inhibitor
  - Elbasvir is an NS5A inhibitor
- Dose
  - 100 / 50 mg (grazoprevir / elbasvir) once daily
- AE: fatigue and headache, rare (0.8%) elevated ALT
- Metabolized by CYP3A4



- Eliminated in bile and feces
  - Contraindicated in Child-Pugh B or C (elbasvir → ↓ grazoprevir)
  - No renal dose changes
  - CYP3A and P-gp inducers will ↓ concentration and are contraindicated, and strong CYP3 inhibitors (boosted protease inhibitors, azole antifungals) will ↑ concentration and are not recommended
  - Low risk of med-med interaction, but CYP3A (grazoprevir) and P-gp inhibitor (elbasvir) so causing with meds that use both (e.g., tacrolimus, some statins, dabigatran, ticagrelor).
  - Nucleotide reverse transcriptase inhibitors can be used with zepatier - abacavir, lamivudine, tenofovir (tenofovir disoproxil fumarate or as tenofovir alafenamide), emtricitabine, rilpivirine, raltegravir, dolutegravir and maraviroc
- ❖ Daclatasvir (with Sofosbuvir - Darvoni) – Genotype 1-6 (add ribavirin for genotype 3)
- MOA
    - NS5A inhibitor
  - Dose
    - 30 or 60 mg once daily
  - AE
    - Fatigue, headache, nausea
  - Eliminated in feces (90%, 10% urine)
  - No hepatic or renal dose changes
  - Reduce dose to 30 if pts on aibiotics: clarithromycin, telithromycin, erythromycin and antifungals ketoconazole, itraconazole, posaconazole and voriconazole. Also if HAART for HIV with darunavir

### Specific Drugs

- ❖ Sofosbuvir (Sovaldi) – Taken in combination as below
- MOA
    - NS5B polymerase inhibitor
  - Dose
    - 400mg once daily
  - AE
    - Most common fatigue and headache (when given with ribavirin) and nausea, insomnia, anemia and mild elevated amylase, lipase, and CK (when given with ribavirin and peg-IFN)
  - 80% renal excretion, 15% fecal
  - Caution if eGFR < 30
  - Contraindicated if patient on amiodarone due to life threatening arrhythmias
    - If change amiodarone then wait 3 months before started treatment with sofosbuvir due to long half life of amiodarone.
  - Transported by P-glycoprotein
    - ↓ concentration with P-gp inducers (rifampin, carbamazepine, phenytoin)
  - No drug-drug interaction with other DAA



❖ Sofosbuvir / Ledipasvir (Harvoni) – Genotype 1, 4, 5, 6

- MOA: NS5A (ledipasvir) and NS5B (sofosbuvir) polymerase inhibitors
- Dose: 400 / 90 mg once daily
- AE: Most common are fatigue and headache (few case reports of severe PAH, but no casual link)
- Ledipasvir 99% biliary excretion, 1% renal, sofosbuvir as above (80% renal)
- Caution if eGFR < 30 (no data for dose adjustment, but higher plasma concentration in these patients)
- Both transported by P-gp so same as above, plus inhibitors of P-gp (amlodipine, carvedilol, cyclosporine, digoxin, dabigatran) warrant caution, but clinical consequences unlikely (as per article nothing sited)
- Contraindicated with amiodarone
- Not recommended with rosuvastatin
  - Monitor with other statins (inhibition of OATP-organic anion transporting protein by ledipasvir)
- ↓ concentration with ↑ gastric pH
  - Caution in those on high dose H2 or PPI (lower SVR in those on high dose PPI)
- Can use with all antiretrovirals
  - Caution if used with tenofovir plus pharmacokinetic enhancers (ritonavir or cobicistat)

❖ Sofosbuvir and velpatasvir (Epclusa) – Genotype 1-6

- MOA: NS5A inhibitor (velpatasvir) and NS5B polymerase inhibitor (sofosbuvir)
- Dose: 400 / 100 mg once daily
- AE: Headache, fatigue, nausea (similar rates to placebo)
- Velpatasvir mostly excreted through bile
- Contraindicated with P-gp or CYP inducers (rifampicin, rifabutin, carbamazepine, phenobarbital, phenytoin, St John's wort, modafinil) as it will decrease concentration and effect
- Considered safe with P-gp, BCRP, OATP and CYP inhibitors, but need to be cautious (digoxin, dabigatran, ticagrelor, carvedilol, amlodipine, diltiazem, aliskiren)
- Like above, ↑ solubility decreases with ↑ stomach pH
  - Not to be administered with high dose PPI (no > 20mg omeprazole, panto 40, also 30)
  - If must then give with food and 4 hrs before PPI
- Like above, can use with all antiretrovirals, but
  - Caution if used with tenofovir, monitor renal function

❖ Simeprevir (Olysio) – Genotype 1 and 4

- MOA: NS3 / 4A
- Dose: 150mg once daily
- AE
  - Rash (photosensitivity), pruritus, nausea



- Metabolized by CYP3A4
  - Excreted in bile
  - Not recommended in Child-Pugh B and contraindicated in C
  - No renal dose changes
  - Contraindicated with anticonvulsants (carbamazepine, oxcarbazepine, phenobarbital, phenytoin), antibiotics (erythromycin, clarithromycin, telithromycin), antimycobacterials (rifampin, rifabutin, rifapentine), antifungals (itraconazole, ketoconazole, posaconazole, fluconazole, voriconazole), dexamethasone, cisapride, herbal products (milk thistle, St John's wort) and a number of antiretroviral drugs (cobicistat-based regimens, efavirenz, etravirine, nevirapine, ritonavir, and any HIV protease inhibitor)
  - Dose adjustments are needed with some antiarrhythmics, warfarin, calcium channel blockers, HMG Co-A reductase inhibitors and sedative / anxiolytics.
  - Safe with Raltegravir, maraviroc, rilpivirine, tenofovir, emtricitabine, lamivudine and abacavir
- ❖ Ribavirin
- MOA
  - Dose: 400 mg qAM, 600 mg qPM (<75 kg), 600 mg BID (>75 kg)
    - 1000 mg or 1200 mg respectively split dose
  - AE
    - Rash, cough, hemolytic anemia, teratogenic / embryogenic complications (women of childbearing age and their partners should use contraception for 6 months post treatment)
  - Renal dosing in severe renal insufficiency and ESRD patients

USE: [www.hep-druginteractions.org](http://www.hep-druginteractions.org) to check drug-drug interactions

## Genotype I

### Hepatitis C patients without cirrhosis and patients with compensated (Child-Pugh A) cirrhosis

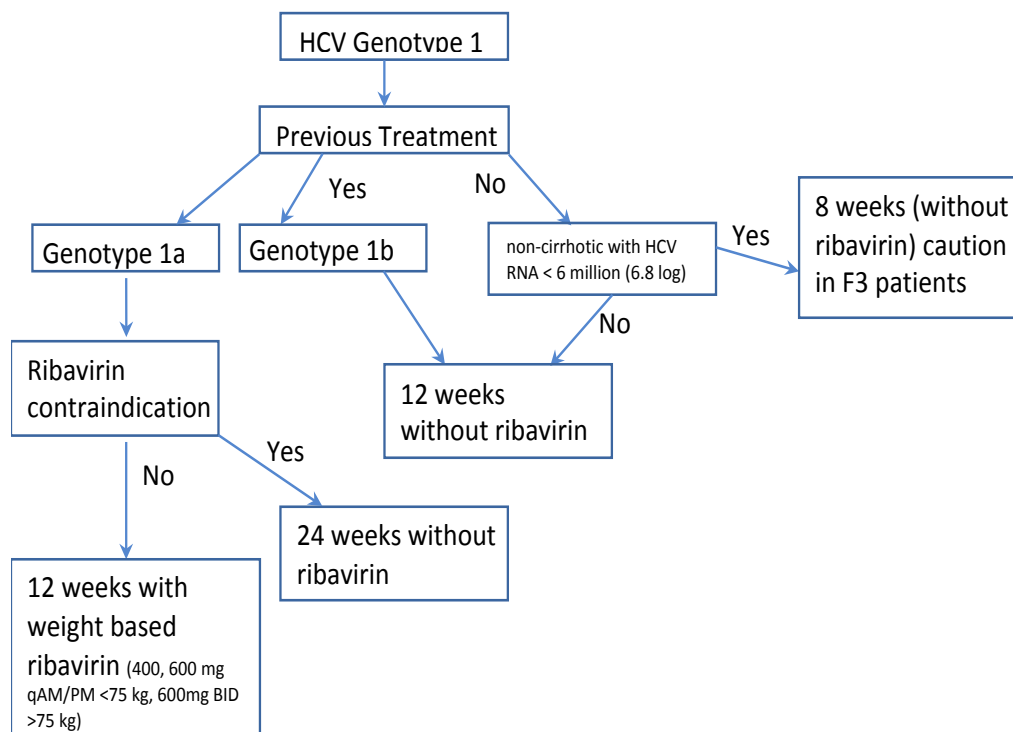
- IFN-free combination treatment regimens available as valuable options for each HCV genotype
- IFN-free combination treatment regimens available as valuable options for each options for each HCV genotype.

| Combination regimen                                 | Genotype 1 | Genotype 2 | Genotype 3 | Genotype 4 | Genotype 5 and 6 |
|-----------------------------------------------------|------------|------------|------------|------------|------------------|
| – Sofosbuvir + ribavirin                            | No         | Suboptimal | Suboptimal | No         | No               |
| – Sofosbuvir / leipasvir ± ribavirin                | Yes        | No         | No         | Yes        | Yes              |
| – Sofosbuvir / velpatasvir ± ribavirin              | Yes        | Yes        | Yes        | Yes        | Yes              |
| – Ombitasvir / velpatasvir / ritonavir ± ribavirin  | Yes        | No         | No         | No         | No               |
| – Ombitasvir / paritaprevir / ritonavir ± ribavirin | No         | No         | No         | Yes        | No               |
| – Grazoprevir / elbasvir ± ribavirin                | Yes        | No         | No         | Yes        | No               |
| – Sofosbuvir + daclatasvir ± ribavirin              | Yes        | Yes        | Yes        | Yes        | Yes              |
| – Sofosbuvir + simeprevir ± ribavirin               | Suboptimal | No         | No         | Yes        | No               |



- Indications for HCV treatment in HCV / HIV co-infected persons are identical to those in patients with HCV mono-infection (**A1**).
- IFN-free regimens are the best options in HCV-mono-infected and in HIV-co-infected patients without cirrhosis or with compensated (Child- Pugh A) cirrhosis, because of their virological efficacy, ease of use and tolerability (**A1**).
- Treatment alterations or dose adjustments may be needed in case of interactions with antiretroviral drugs (**A1**).

❖ Option #1: Harvoni (Sofosbuvir / Ledipasvir) – from ION-1,2,3, and 4 trials



\*\*\* If reliable NS5A resistance testing is performed

- Treatment-experienced, DAA-naïve patients infected with genotype 1a with or without compensated cirrhosis who have NS5A RASs that confer high-level resistance to ledipasvir (M28A/G/T, Q30E/G/H/K/R, L31M/V, P32L/S, H58D, and/or Y93C/H/N/S) detected at baseline should be treated with the fixed-dose combination of sofosbuvir and ledipasvir for 12 weeks with ribavirin
- Those without ledipasvir RASs at baseline can be treated with the fixed-dose combination of sofosbuvir and ledipasvir for 12 weeks without ribavirin (**B1**).

- IFN-free combinations to treat all genotypes (1 to 6) of HCV
  - Sofosbuvir +/- ribavirin
  - Sofosbuvir + daclatasvir +/- ribavirin



**Patients with severe liver disease with or without an indication for liver transplantation, HCC, or co-infection and patients in the post-liver transplant setting**

- ❖ *Patients with decompensated cirrhosis and no contraindication for transplant and no HCC*
  - Patients with decompensated cirrhosis without HCC awaiting liver transplantation with a MELD score <18-20
    - Treat prior to liver transplantation
    - Treatment should be initiated as soon as possible in order to complete a full treatment course before transplantation and assess the effect of viral clearance on liver function, because significant improvement in liver function may lead to delisting selected cases (B1).
  - Protease inhibitors (NS3/4A) should not be used in patients with Child-Pugh B or C decompensated cirrhosis (A1). Due to higher drug levels which can cause toxicity.
  - Treat with one of the following combinations
    - Sofosbuvir and ledipasvir, sofosbuvir and velpatasvir, or sofosbuvir and daclatasvir, with daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or ≥75 kg, respectively)
    - Ribavirin started at the dose of 600 mg daily and
    - The dose subsequently adjusted depending on tolerance (A1).
  - HCV genotype 1, 4, 5 or 6
    - Treat with sofosbuvir and ledipasvir, sofosbuvir and velpatasvir, or sofosbuvir and daclatasvir, for 12 weeks with ribavirin (A1).
  - HCV genotype 2
    - Treat with sofosbuvir and velpatasvir
    - Sofosbuvir and daclatasvir, for 12 weeks with ribavirin (B1).
  - HCV genotype 3 should be treated with sofosbuvir and velpatasvir, or
    - Sofosbuvir and daclatasvir, for 24 weeks with ribavirin (B1)
  - Patients with decompensated cirrhosis with contraindications to the use of ribavirin or with poor tolerance to ribavirin on treatment
    - Treat as above, but for 24 weeks without ribavirin (B1).
  - Patients with decompensated cirrhosis without HCC awaiting liver transplantation with a MELD score ≥18-20
    - Transplant first, without antiviral treatment. HCV infection should be treated after liver transplantation (B1)
  - Patients with decompensated cirrhosis without HCC awaiting liver transplantation with a MELD score ≥18-20
    - Treat before transplantation if the waiting time on the transplant list exceeds 6 months, depending on the local situation (B1)



❖ *Patients with decompensated cirrhosis without an indication for liver transplantation*

- Decompensated cirrhosis (Child-Pugh B and Child-Pugh C up to 12 points) not on the waiting list for liver transplantation and without concomitant comorbidities that could impact their survival should be treated urgently (A1).
- Protease inhibitors not recommended in Child- Pugh B and contraindicated in Child-Pugh C (A1).
- Treated as above
- If contraindications to ribavirin or poor tolerance then fixed-dose combination of sofosbuvir and ledipasvir (genotypes 1, 4, 5 or 6), sofosbuvir and velpatasvir (all genotypes), or the combination of sofosbuvir and daclatasvir (all genotypes) for 24 weeks without ribavirin (B2).
- Due to the limited amount of safety data reported in patients with decompensated cirrhosis, frequent clinical and laboratory assessment is necessary (B2).

❖ *Patients with HCC, without cirrhosis or with compensated cirrhosis, with an indication for liver transplantation*

- In patients with HCC awaiting liver transplantation with an indication for antiviral treatment
  - Initiate as soon as possible in order to complete a full treatment course before transplantation (B1)
- Patients with HCC who have no or compensated (Child-Pugh A) cirrhosis awaiting liver transplantation
  - Treat prior to liver transplantation, according to the general recommendations in patients with no or compensated cirrhosis and no HCC (B1)
- No discussion regarding HCC with decompensated cirrhosis and indication for Tx, but can infer from above an below to wait until transplant in this case.

❖ *Patients with HCC without an indication for liver transplantation*

- Long-term benefit of antiviral therapy to reduce risk of HCC in patients undergoing resection or ablation is unknown
  - These patients frequently have advanced fibrosis and should receive appropriate antiviral therapy for their liver disease according to the HCV genotype, prior therapy (B2).
  - Data not strong and mostly inferred from INF treatment showing improved outcomes post ablation / resection.

❖ *Post Liver Transplant Re-Occurrence*

- Treatment should be initiated early after liver transplantation, ideally as early as possible when the patient is stabilized (generally after the first 3 months post-transplant), because
  - The SVR12 rates diminish in patients with advanced post-transplant liver disease (A1)
- Acute cholestatic hepatitis or the presence of moderate to extensive fibrosis or portal hypertension one year after transplantation
  - Predict ↓ disease progression and ↓ graft loss
  - Indicate urgent antiviral treatment (A1)





- Patients with post-transplant recurrence of HCV genotype 1, 4, 5 or 6 infection with or without cirrhosis, treat with
    - Sofosbuvir and ledipasvir
    - Sofosbuvir and daclatasvir for 12 weeks with daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or ≥75 kg, respectively), without the need for immunosuppressant drug dose adjustments (with the probable exception of everolimus) (A1)
  - Patients with post-transplant recurrence of HCV genotype 2 with or without cirrhosis
    - Treat with sofosbuvir and daclatasvir for 12 weeks with daily weight-based ribavirin, without the need for immunosuppressant drug dose adjustments (with the probable exception of everolimus) (B1)
  - Patients with post-transplant recurrence of HCV genotype 3
    - Treated with sofosbuvir and daclatasvir for 24 weeks regardless of the stage of liver disease, with daily weight-based ribavirin, without the need for immunosuppressant drug dose adjustments (with the probable exception of everolimus) (B1)
  - Patients with post-transplant recurrence of all HCV genotypes without cirrhosis (F0-F3), with compensated (Child-Pugh A) cirrhosis or with decompensated (Child-Pugh B or C) cirrhosis
    - Treat with sofosbuvir and velpatasvir for 12 weeks (24 weeks in patients with genotype 3 and decompensated (Child-Pugh B or C) cirrhosis) with daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or ≥75 kg, respectively), as soon as the results of ongoing studies, particularly drug-drug interactions with immunosuppressant drugs, have been presented (C2)
  - Patients with decompensated cirrhosis
    - Ribavirin started at the dose of 600 mg daily, and the dose subsequently adjusted depending on tolerance (B1)
  - Patients with contraindications to the use of ribavirin or with poor tolerance to ribavirin on treatment
    - Sofosbuvir and ledipasvir (genotypes 1, 4, 5 or 6), sofosbuvir and velpatasvir (all genotypes), or sofosbuvir and daclatasvir (all genotypes) for 24 weeks without ribavirin (B1)
- ❖ *HBV Co-infection*
- Treat the same as without, add hep B treatment if HBsAg and DNA positive
- ❖ *Immune complex-mediated manifestations of chronic hepatitis C*
- Antiviral therapy mixed cryoglobulinemia and renal disease associated with chronic HCV infection (B1).
  - The indication of rituximab in HCV-related renal disease
    - Discuss with multidisciplinary team (B1). It is also used for both skin and organ involvement in cyro



### ❖ *Renal Failure Patients*

- No change if eGFR > 30
- If eGFR <30 and patients with ESRD on hemodialysis
  - Sofosbuvir should be used with caution because concentration increases in these patients (renal excretion) and no dose known for this pt group (B1)
- HCV genotype 1a ritonavir-boosted paritaprevir, ombitasvir and dasabuvir for 12 weeks or grazoprevir and elbasvir for 12 weeks, with daily ribavirin (200 mg/ day) if the haemoglobin level is >10 g/dl at baseline (B1).
- HCV genotype 1b ritonavir-boosted paritaprevir, ombitasvir and dasabuvir for 12 weeks or grazoprevir and elbasvir for 12 weeks, without ribavirin (A1).
- HCV genotype 4 ritonavir-boosted paritaprevir and ombitasvir for 12 weeks with daily ribavirin (200 mg/day) if the haemoglobin level is >10 g/dl at baseline, or grazoprevir and elbasvir for 12 weeks without ribavirin (B1).
- In patients receiving ribavirin
  - Hemoglobin levels should be carefully and frequently monitored and ribavirin administration should be interrupted in case of severe anaemia (haemoglobin < 85).
  - The use of erythropoietin and, eventually, blood transfusion, may be useful in patients with severe ribavirin-induced anaemia (B1).
- Patients with cirrhosis, and those with a contraindication or who do not tolerate ribavirin,
  - May benefit from 24 weeks of these therapies without ribavirin (B2)
- If treatment is urgently needed in patients with severe renal impairment (eGFR <30 mL/min/1.73 m<sup>2</sup>) or with end-stage renal disease on haemodialysis without an indication for kidney transplantation infected with HCV genotype 2
  - Sofosbuvir and velpatasvir, or
  - Sofosbuvir and daclatasvir for 12 weeks without ribavirin
  - Renal function may worsen and should be carefully monitored and treatment should be interrupted immediately in case of deterioration (B1)
- As above, but HCV genotype 3, these patients should receive
  - Sofosbuvir and velpatasvir, or
  - Sofosbuvir and daclatasvir for 12 weeks with daily ribavirin (200 mg/day) if the haemoglobin level is >10 g/dL at baseline, or for 24 weeks without ribavirin
  - Renal function may worsen and should be carefully monitored and treatment should be interrupted immediately in case of deterioration (B1).
- The risks versus benefits of treating patients with end-stage renal disease and an indication for kidney transplantation before or after renal transplantation
  - Individual assessment (B2)
  - Can transplant and then treat in kidney transplant patients

### ❖ *Non-hepatic solid organ transplant recipients*

- Solid organ transplant recipients, including kidney, heart, lung, pancreas or small bowel recipients should be treated for their HCV infection after transplantation, provided that their life expectancy exceeds one year (A1).
  - Very limited data with heart, case reports with lung, none with pancreas or SB



- HCV genotype 1, 4, 5 or 6 infection sofosbuvir and ledipasvir, sofosbuvir and velpatasvir (if the drug-drug interaction profile with immunosuppressants is favourable in ongoing studies), or sofosbuvir and daclatasvir, without the need for immunosuppressant drug dose adjustments (with the probable exception of everolimus) (B1).
- HCV genotype 2, or 3 sofosbuvir or velpatasvir or sofosbuvir and daclatasvir (B1).

❖ *Active PWID or substitute meds*

- PWIDs should be routinely and voluntarily tested for anti-HCV antibodies and if negative, annually (A1).
- Minimize risk of infection and re-infection, 1-8% / year in PWID or MSM (B1).
- A history of intravenous drug use and recent drug use at treatment initiation are not associated with reduced SVR, but ongoing users with psychiatric history have lower adherence and SVR
  - Decisions to treat must be made on a case-by-case basis (B1)
- The anti-HCV regimens that can be used in PWIDs are the same as in non-PWIDs.
  - They do not require specific methadone and buprenorphine dose adjustment,
  - Monitoring for signs of opioid toxicity or withdrawal should be undertaken (B1).
- Opioid substitution therapy is not a contraindication for liver transplantation and
  - Individuals on opioid substitution should not be advised to reduce or stop therapy (B1)

## Treatment Monitoring

❖ *General*

- In patients treated with an IFN-free regimen
  - HCV RNA or HCV core antigen levels should be measured at baseline, between week 2 and 4 for assessment of adherence (optional), at end-of-treatment (week 8, 12, 16 or 24 in patients treated 8, 12, 16 or 24 weeks, respectively), and 12 or 24 weeks after the end of therapy (SVR12 or SVR24, respectively) (A2).
- Can be simplify in order to improve access to care by measuring HCV RNA or HCV core antigen levels only at baseline and 12 or 24 weeks after the end of therapy (SVR12 or SVR24, respectively) (A2).

❖ *Monitoring of treatment and safety*

- Patients receiving an IFN-free regimen should be assessed for clinical side effects at each visit (A1).
  - Side effects are rare and minimal as discussed above.
- Hematological side effects should be assessed at weeks 2 and 4 of therapy and at 4 to 8 week intervals thereafter in patients receiving ribavirin (A1).
- ALT levels should be assessed at weeks 4, 8 and 12 of therapy, and at week 24 if 24 weeks of treatment, as well as at 12 or 24 weeks post-treatment (A1).
- An ↑ in ALT levels on treatment should prompt a test for HBs antigen and / or HBV DNA (B1).



- Renal function should be checked regularly in patients receiving sofosbuvir, especially in those with reduced eGFR (A1).
- Monitoring for rashes and indirect bilirubin elevations without ALT elevations should be performed in patients receiving simeprevir (A1).
- Monitoring for indirect bilirubin increases should be performed in patients receiving the combination of ritonavir-boosted paritaprevir, ombitasvir and dasabuvir (A1).

❖ *Post-treatment follow-up of patients who achieve an SVR*

- Non-cirrhotic patients with SVR should be retested for ALT and HCV RNA (or HCV core antigen) at 48 weeks post-treatment, then discharged if ALT is normal and HCV RNA is negative (A1).
- Patients with advanced fibrosis (F3) and cirrhotic patients with SVR should undergo surveillance for HCC every 6 months by means of ultrasound (A1).
  - As well as continued portal hypertension and varices screening if varices present at pre-treatment endoscopy (though index variceal bleed is seldom seen in low-risk patients after the achievement of SVR) (A2).
- Following SVR, monitoring for HCV reinfection through annual HCV RNA assessment should be undertaken in people who inject drugs or men who have sex with men (MSM) with ongoing risk behaviour (A1).

❖ *Retreatment of non-sustained virological responders*

- Patients who failed after pegylated IFN- $\alpha$  and ribavirin combination treatment must be retreated according to the above recommendations by HCV genotype (A1).
- HCV genotype 1 who failed after a triple combination regimen of pegylated IFN- $\alpha$ , ribavirin and telaprevir, boceprevir or simeprevir
  - Retreat with the IFN-free combination of
    - Sofosbuvir and ledipasvir, sofosbuvir and velpatasvir, or
    - Sofosbuvir and daclatasvir, with ribavirin for 12 weeks (A1)
- Patients who failed on a DAA-containing regimen
  - Retreat with an IFN-free regimen for 12 weeks with weight-based ribavirin if they have no, mild or moderate fibrosis (METAVIR score F0 to F2), for 24 weeks with ribavirin if they have extensive fibrosis (F3) or cirrhosis, unless otherwise specified below (B1)
- Patients who fail on sofosbuvir alone or sofosbuvir plus ribavirin or sofosbuvir plus pegylated IFN- $\alpha$  and ribavirin
  - Retreat with a combination of
    - Sofosbuvir and ledipasvir (genotypes 1, 4, 5 or 6)
    - Sofosbuvir and velpatasvir (all genotypes)
    - Ritonavir-boosted paritaprevir
    - Ombitasvir and dasabuvir (genotype 1)
    - Ritonavir- boosted paritaprevir and ombitasvir (genotype 4)
    - Grazoprevir and elbasvir (genotypes 1 or 4; 24 weeks in F0-F2 patients with HCV RNA >800,000 IU/mL), sofosbuvir plus daclatasvir (all genotypes), or sofosbuvir plus simeprevir (genotype 4) (B2).



- Patients infected with genotype 1 or 4 who fail on a regimen containing sofosbuvir and simeprevir
  - Retreat with a combination of
    - Sofosbuvir with ledipasvir
    - Sofosbuvir and velpatasvir, or sofosbuvir and daclatasvir (B1).
- Patients infected with HCV genotype 1 or 4 who fail on a regimen containing an NS5A inhibitor, such as ledipasvir, velpatasvir, ombitasvir, elbasvir or daclatasvir
  - Retreat with a combination of
    - Sofosbuvir, ritonavir-boosted paritaprevir, ombitasvir and dasabuvir (genotype 1),
    - Sofosbuvir, ritonavir-boosted paritaprevir and ombitasvir (genotype 4),
    - Sofosbuvir, grazoprevir and elbasvir (genotypes 1 and 4) or
    - Sofosbuvir, simeprevir and daclatasvir (genotypes 1 or 4), for 12 weeks (genotype 1b or 4 patients with METAVIR score F0 to F2) or 24 weeks (all patients with genotype 1a; genotype 1b and 4 patients with METAVIR score F3 or with compensated cirrhosis) with ribavirin.
  - Treatment should be administered with caution in patients with extensive fibrosis (METAVIR score F3) or compensated cirrhosis due to a possible risk of severe adverse events of some of these combinations (B1).
- Patients infected with HCV genotype 2, 3, 5 or 6 who fail on a regimen containing an NS5A inhibitor, such as ledipasvir, velpatasvir or daclatasvir
  - Retreated with a combination of sofosbuvir and velpatasvir for 24 weeks with ribavirin (B1)
  - Alternatively, patients without an urgent need for treatment can wait until more data and / or alternative therapeutic options become available (A1).
- The utility of HCV resistance testing prior to retreatment in patients who failed on any of the DAA-containing treatment regimens is unknown.
  - If reliable resistance testing is performed, retreatment can be guided by probabilities of response according to the resistance profile observed in the context of an experienced multidisciplinary team (B2).

#### ❖ Treatment of Acute Hep C

- Patients with acute hepatitis C should be treated with a combination of
  - Sofosbuvir and ledipasvir (genotypes 1, 4, 5 and 6)
  - Sofosbuvir and velpatasvir (all genotypes)
  - Sofosbuvir and daclatasvir (all genotypes) for 8 weeks without ribavirin (B1)



### ➤ Drug Interactions

Treatment recommendations for HCV-monoinfected or HCV / HIV co-infected patients with chronic hepatitis C without cirrhosis, including treatment-naïve patients and patients who failed on a treatment based on pegylated IFN- $\alpha$  and ribavirin (treatment-experienced, DAA-naïve patients).

| Patients        | Treatment-naïve or – experienced | Sofosbuvir/ledipasvir                       | Sofosbuvir/velpatasvir                      | Ombitasvir/Paritaprevir/Ritonavir and dasabuvir | Ombitasvir/Paritaprevir/Ritonavir | Grazoprevir/velbasvir                                                                                                       | Sofosbuvir and daclatasvir                   | Sofosbuvir and simeprevir                  |
|-----------------|----------------------------------|---------------------------------------------|---------------------------------------------|-------------------------------------------------|-----------------------------------|-----------------------------------------------------------------------------------------------------------------------------|----------------------------------------------|--------------------------------------------|
| Genotype 1a     | Treatment – naïve                | 8-12 wk, no ribavirin                       | 12 wk, no ribavirin                         | 12 wk no ribavirin                              | No                                | 12 wk, no ribavirin, if HCV RNA $\leq$ 800,000 (5.9 log) IU/mL or 16 wk with ribavirin if HCV RNA > 800,000 (5.9 log) IU/mL | 12 wk, no ribavirin                          | No                                         |
|                 | Treatment experienced            | 12 wk with ribavirin or 24 wk, no ribavirin |                                             |                                                 |                                   |                                                                                                                             | 12 wk with ribavirin* or 24 wk, no ribavirin |                                            |
| Genotype 1b     | Treatment-naïve                  | 8-12 wk, no ribavirin                       | 12 wk, no ribavirin                         | 8-12 wk, no ribavirin                           | No                                | 12 wk, no ribavirin                                                                                                         | 12 wk, no ribavirin                          | No                                         |
|                 | Treatment experienced            | 12 wk, no ribavirin                         |                                             | 12 wk, no ribavirin                             |                                   |                                                                                                                             |                                              |                                            |
| Genotype 2      | Both                             | No                                          | 12 wk, no ribavirin                         | No                                              | No                                | No                                                                                                                          | 12 wk, no ribavirin                          | No                                         |
| Genotype 3      | Treatment-naïve                  | No                                          | 12 wk, no ribavirin                         | No                                              | No                                | No                                                                                                                          | 12 wk, no ribavirin                          | No                                         |
|                 | Treatment experienced            |                                             | 12 wk with ribavirin or 24 wk, no ribavirin |                                                 |                                   |                                                                                                                             | 12 wk with ribavirin or 24 wk, no ribavirin  |                                            |
| Genotype 4      | Treatment-naïve                  | 12 wk, no ribavirin                         | 12 wk, no ribavirin                         | No                                              | 12 wk, no ribavirin               | 12 wk, no ribavirin                                                                                                         | 12 wk, no ribavirin                          | 12 wk, no ribavirin                        |
|                 | Treatment experienced            | 12 wk with ribavirin or 24 wk, no ribavirin |                                             |                                                 |                                   | 12 wk, no ribavirin if HCV RNA $\leq$ 800,000 (5.9 log) IU/mL or 16 wk with ribavirin if HCV RNA > 800,000 (5.9 log) IU/mL  | 12 wk, no ribavirin or 24 wk, no ribavirin   | 12 wk, no ribavirin or 24 wk, no ribavirin |
| Genotype 5 or 6 | Treatment-naïve                  | 12 wk, no ribavirin                         | 12 wk, no ribavirin                         | No                                              | No                                | No                                                                                                                          | 12 wk, no ribavirin                          | No                                         |
|                 | Treatment experienced            | 12 wk with ribavirin or 24 wk, no ribavirin |                                             |                                                 |                                   |                                                                                                                             | 12 wk with ribavirin or 24 wk, no ribavirin  |                                            |

<sup>a</sup>Add ribavirin only in patients with RASs that confer high-level resistance to NS5A inhibitors at baseline if RAS testing available

<sup>b</sup>Prolong to 16 weeks and add ribavirin only in patients with RASs that confer resistance to elbasvir at baseline if RAS testing available

<sup>c</sup>Add ribavirin only in patients with NS5A RAS Y93H at baseline if RAS testing available



Treatment recommendations for HCV-moninfected or HCV / HIV co-infected patients with chronic hepatitis C with compensated (Child-Pugh A), cirrhosis, including treatment-naïve patients and patients who failed on a treatment based on pegylated IFN- $\alpha$  and ribavirin (treatment-experienced, DAA-naïve patients).

| Patients        | Treatment-naïve or -experienced | Sofosbuvir/ledipasvir                       | Sofosbuvir/velpatasvir                      | Ombitasvir/Paritaprevir/Ritonavir and dasabuvir | Ombitasvir/Paritaprevir/Ritonavir | Greziprevir/elbasvir                                                                                                        | Sofosbuvir and daclatasvir                   | Sofosbuvir and simeprevir                    |
|-----------------|---------------------------------|---------------------------------------------|---------------------------------------------|-------------------------------------------------|-----------------------------------|-----------------------------------------------------------------------------------------------------------------------------|----------------------------------------------|----------------------------------------------|
| Genotype 1a     | Treatment-naïve                 | 12 wk, no ribavirin                         | 12 wk, no ribavirin                         | 12 wk with ribavirin                            | No                                | 12 wk, no ribavirin, if HCV RNA $\leq$ 800,000 (5.9 log) IU/mL or 16 wk with ribavirin if HCV RNA > 800,000 (5.9 log) IU/mL | 12 wk, no ribavirin                          | No                                           |
|                 | Treatment experienced           | 12 wk with ribavirin or 24 wk, no ribavirin |                                             |                                                 |                                   |                                                                                                                             | 12 wk with ribavirin* or 24 wk, no ribavirin |                                              |
| Genotype 1b     | Treatment-naïve                 | 12 wk, no ribavirin                         | 12 wk, no ribavirin                         | 12 wk, no ribavirin                             | No                                | 12 wk, no ribavirin                                                                                                         | 12 wk, no ribavirin                          | No                                           |
|                 | Treatment experienced           |                                             |                                             |                                                 |                                   |                                                                                                                             |                                              |                                              |
| Genotype 2      | Both                            | No                                          | 12 wk, no ribavirin                         | No                                              | No                                | No                                                                                                                          | 12 wk, no ribavirin                          | No                                           |
| Genotype 3      | Treatment-naïve                 | No                                          | 12 wk with ribavirin or 24 wk, no ribavirin | No                                              | No                                | No                                                                                                                          | 12 wk, with ribavirin                        | No                                           |
|                 | Treatment experienced           |                                             |                                             |                                                 |                                   |                                                                                                                             |                                              |                                              |
| Genotype 4      | Treatment-naïve                 | 12 wk, no ribavirin                         | 12 wk, no ribavirin                         | No                                              | 12 wk, with ribavirin             | 12 wk, no ribavirin                                                                                                         | 12 wk, no ribavirin                          | 12 wk, no ribavirin                          |
|                 | Treatment experienced           | 12 wk with ribavirin or 24 wk, no ribavirin |                                             |                                                 |                                   | 12 wk, no ribavirin if HCV RNA $\leq$ 800,000 (5.9 log) IU/mL or 16 wk with ribavirin if HCV RNA > 800,000 (5.9 log) IU/mL  | 12 wk, with ribavirin or 24 wk, no ribavirin | 12 wk, with ribavirin or 24 wk, no ribavirin |
| Genotype 5 or 6 | Treatment-naïve                 | 12 wk, no ribavirin                         | 12 wk, no ribavirin                         | No                                              | No                                | No                                                                                                                          | 12 wk, no ribavirin                          | No                                           |
|                 | Treatment experienced           | 12 wk with ribavirin or 24 wk, no ribavirin |                                             |                                                 |                                   |                                                                                                                             | 12 wk with ribavirin or 24 wk, no ribavirin  |                                              |

<sup>a</sup>Add ribavirin only in patients with RASs that confer high-level resistance to NS5A inhibitors at baseline if RAS testing available

<sup>b</sup>Prolong to 16 weeks and add ribavirin only in patients with RASs that confer resistance to elbasvir at baseline if RAS testing available

<sup>c</sup>Add ribavirin only in patients with NS5A RAS Y93H at baseline if RAS testing available





- ❖ Option #2: Epclusa (Sofosbuvir / Velpatasvir) – from ASTRAL-1 trial
  - Fixed dose combination of sofosbuvir (400 mg) and velpatasvir (100 mg) in a single tablet administered once daily (A1).
  - Treatment-naïve and treatment-experienced patients with or without compensated cirrhosis should be treated with the fixed-dose combination of sofosbuvir and velpatasvir for 12 weeks without ribavirin (A1).
- ❖ Option #3: Ritonavir-boosted paritaprevir, ombitasvir and dasabuvir (Viekira) – from SAPPHIRE 1 and 2
  - Genotype 1 can be treated with the fixed-dose combination of ombitasvir (12.5 mg), paritaprevir (75 mg) and ritonavir (50 mg) in one single tablet (two tablets once daily with food), and dasabuvir (250 mg) (one tablet twice daily) (A1).
  - Subtype 1b with or without compensated cirrhosis
    - Combination of ombitasvir, paritaprevir and ritonavir plus dasabuvir for 12 weeks without ribavirin (A1)
  - Treatment-naïve patients infected with subtype 1b without cirrhosis
    - The combination of ombitasvir, paritaprevir and ritonavir plus dasabuvir for 8 weeks without ribavirin, with caution in patients with F3 fibrosis (B1)
  - Patients infected with subtype 1a without cirrhosis
    - Combination of ombitasvir, paritaprevir and ritonavir plus dasabuvir for 12 weeks with daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or ≥75 kg, respectively) (A1)
  - Patients infected with subtype 1a with compensated cirrhosis
    - Combination of ombitasvir, paritaprevir and ritonavir plus dasabuvir for 24 weeks with daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or ≥75 kg, respectively) (A1)
- ❖ Option #4: Grazoprevir / elbasvir (Zepatier) – from C-EDGE-TN / CO-INFECTION / TE
  - Fixed dose combination of grazoprevir (100 mg) and elbasvir (50 mg) in a single tablet administered once daily (A1).
  - Treatment-naïve and treatment-experienced subtype 1b patients with or without compensated cirrhosis
    - Combination of grazoprevir and elbasvir for 12 weeks without ribavirin (A1)
  - Treatment-naïve and treatment-experienced patients subtype 1a HCV RNA level >800,000 IU/ml (5.9 log<sub>10</sub> IU/ml) 16 weeks with daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or ≥75 kg, respectively).
  - Subtype 1a with an HCV RNA level ≤800,000 IU/ml (5.9 log<sub>10</sub> IU/ml) 12 weeks without ribavirin (B1).
  - If reliable NS5A resistance testing is performed, treatment-naïve and treatment-experienced patients subtype 1a get 16 weeks combo pill with daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or ≥75 kg, respectively)





- If HCV RNA level is >800,000 IU/mL and NS5A RASs that confer resistance to elbasvir (M28A/G/T, Q30D/E/G/H/K/L/R, L31F/M/V, H58D and/or Y93C/H/N/S) are present at baseline.
  - Patients infected with subtype 1a with or without compensated cirrhosis with an HCV RNA level ≤800,000 IU/mL and those with an HCV RNA level >800,000 IU/mL without elbasvir NS5A RASs at baseline should receive the combination of grazoprevir and elbasvir for 12 weeks without ribavirin (B1).
- ❖ **Option #5: Sofosbuvir and daclatasvir (Darvoni)**
  - Combination sofosbuvir (400 mg) in one tablet and daclatasvir (60 mg) in another tablet administered once daily (A1).
  - The dose of daclatasvir must be adjusted to 30 mg in HIV-co-infected patients receiving ritonavir- or cobicistat-boosted atazanavir or cobicistat-boosted elvitegravir, and to 90 mg in HIV co-infected patients receiving efavirenz (B1).
  - Treatment-naïve patients with or without compensated cirrhosis
    - Treat with the combination of sofosbuvir and daclatasvir for 12 weeks without ribavirin (A1)
  - Treatment-experienced, DAA-naïve patients infected with genotype 1b with or without compensated cirrhosis
    - Treat with the combination of sofosbuvir and daclatasvir for 12 weeks without ribavirin (A1)
  - Treatment-experienced, DAA-naïve patients infected with genotype 1a with or without compensated cirrhosis
    - Add daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or ≥75 kg, respectively) 12 weeks (C2)
  - If reliable NS5A resistance testing is performed, treatment-experienced, DAA-naïve patients infected with genotype 1a with or without compensated cirrhosis with NS5A class RASs detected at baseline
    - Treat with the combination of sofosbuvir and daclatasvir for 12 weeks with ribavirin
    - Those without NS5A class RASs at baseline can be treated with the combination of sofosbuvir and daclatasvir for 12 weeks without ribavirin (C2)
  - Treatment-experienced, DAA-naïve patients with contraindications to the use of ribavirin or with poor tolerance to ribavirin on treatment
    - Combination of sofosbuvir and daclatasvir for 24 weeks without ribavirin (B1)

## **Genotype 2**

- ❖ **Option #1: Sofosbuvir / velpatasvir (Epclusa) – From ASTRAL-2**
  - Fixed-dose combination of sofosbuvir (400 mg) and velpatasvir (100 mg) in a single tablet administered once daily (A1).
  - Treatment-naïve and treatment-experienced patients with or without compensated cirrhosis should be treated with the fixed-dose combination of sofosbuvir and velpatasvir for 12 weeks without ribavirin (A1).



❖ Option #2: Sofosbuvir and daclatasvir (Darvoni)

- Combination of daily sofosbuvir (400 mg) and daily daclatasvir (60 mg) (B1).
- Treatment-naïve and treatment-experienced patients with or without compensated cirrhosis should be treated with the combination of sofosbuvir and daclatasvir for 12 weeks without ribavirin (B1).

### **Genotype 3**

❖ Option #1: Sofosbuvir / velpatasvir (Epclusa) – ASTRAL-3

- Fixed-dose combination of sofosbuvir (400 mg) and velpatasvir (100 mg) in a single tablet administered once daily, with or without ribavirin (A1).
- Treatment-naïve patients without cirrhosis 12 weeks without ribavirin (A1).
- If no NS5A resistance testing is performed, treatment-experienced patients without cirrhosis or compensated cirrhosis, as well as treatment-naïve with compensated cirrhosis, 12 weeks with daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or ≥75 kg, respectively) (A1).
- If reliable NS5A resistance testing is performed, treatment-experienced patients without cirrhosis, as well as treatment-naïve and treatment-experienced patients with compensated cirrhosis, with the NS5A RAS Y93H detectable at baseline should be treated with the fixed-dose combination of sofosbuvir and velpatasvir for 12 weeks with daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or ≥75 kg, respectively). Patients without the NS5A RAS Y93H at baseline should receive the fixed-dose combination of sofosbuvir and velpatasvir for 12 weeks without ribavirin (A1).
- Patients with contraindications to the use of ribavirin or with poor tolerance to ribavirin on treatment should receive the combination of sofosbuvir and velpatasvir for 24 weeks without ribavirin (C1).

❖ Option #2: Sofosbuvir and daclatasvir (Darvoni)

- Combination of daily sofosbuvir (400 mg) and daily daclatasvir (60 mg) (A1).
- Treatment-naïve patients without cirrhosis 12 weeks without ribavirin (B1).
- If no NS5A resistance testing is performed, treatment-experienced patients without cirrhosis combination sofosbuvir and daclatasvir for 12 weeks with daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or ≥75 kg, respectively) (B1).
- If reliable NS5A resistance testing is performed
  - Treatment- experienced patients without cirrhosis with the NS5A RAS Y93H detectable at baseline combination of sofosbuvir and daclatasvir for 12 weeks with daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or ≥75 kg, respectively). Patients without the NS5A RASs Y93H at baseline should receive the combination of sofosbuvir and daclatasvir for 12 weeks without ribavirin (B1).
- Treatment-naïve and treatment-experienced patients with cirrhosis
  - Combination of sofosbuvir and daclatasvir for 24 weeks with daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or ≥75 kg, respectively) (C1).
- ONLY ONE DIFFERENT THAN ABOVE (compensated cirrhosis above – 12 weeks)



- Patients with contraindications to the use of ribavirin or with poor tolerance to ribavirin on treatment
  - Combination of sofosbuvir and daclatasvir for 24 weeks without ribavirin (C1)

#### **Genotype 4**

- ❖ Option #1: Sofosbuvir / ledipasvir (Harvoni) – SYNERGY trial
  - Fixed- dose combination of sofosbuvir (400 mg) and ledipasvir (90 mg) in a single tablet administered once daily (A1).
  - Treatment-naïve patients with or without compensated cirrhosis 12 weeks without ribavirin (A1).
  - Treatment-experienced patients with or without compensated cirrhosis 12 weeks with daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or ≥75 kg, respectively) (B1).
  - Treatment-experienced patients with or without compensated cirrhosis with contraindications to the use of ribavirin or with poor tolerance to ribavirin 24 weeks without ribavirin (B1).
- ❖ Option #2: Sofosbuvir / velpatasvir (Epclusa) – ASTRAL-1 trial
  - Fixed- dose combination of sofosbuvir (400 mg) and velpatasvir (100 mg) in a single tablet administered once daily (A1).
  - Treatment-naïve and treatment-experienced patients with or without compensated cirrhosis should 12 weeks without ribavirin (A1).
- ❖ Option #3: Ombitasvir / paritaprevir / ritonavir (Viekira) – PEARL-1, AGATE-1 trials
  - Fixed-dose combination of ombitasvir (12.5 mg), paritaprevir (75 mg) and ritonavir (50 mg) in one single tablet (two tablets once daily with food), without dasabuvir (A1).
  - Treatment with and without compensated cirrhosis 12 weeks with daily weight- based ribavirin (1000 or 1200 mg in patients <75 kg or ≥75 kg, respectively) (A1).
- ❖ Option #4: Grazoprevir / elbasvir (Zepatier) – EDGE trials
  - Fixed- dose combination of grazoprevir (100 mg) and elbasvir (50 mg) in a single tablet administered once daily (A1).
  - Treatment-naïve patients with or without compensated cirrhosis 12 weeks without ribavirin (A1).
  - Treatment-experienced patients with or without compensated cirrhosis with an HCV RNA level at baseline >800,000 IU/mL 16 weeks with daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or ≥75 kg, respectively) (B2). If <800,000 then 12 weeks without ribavirin (from genotype 1 data).



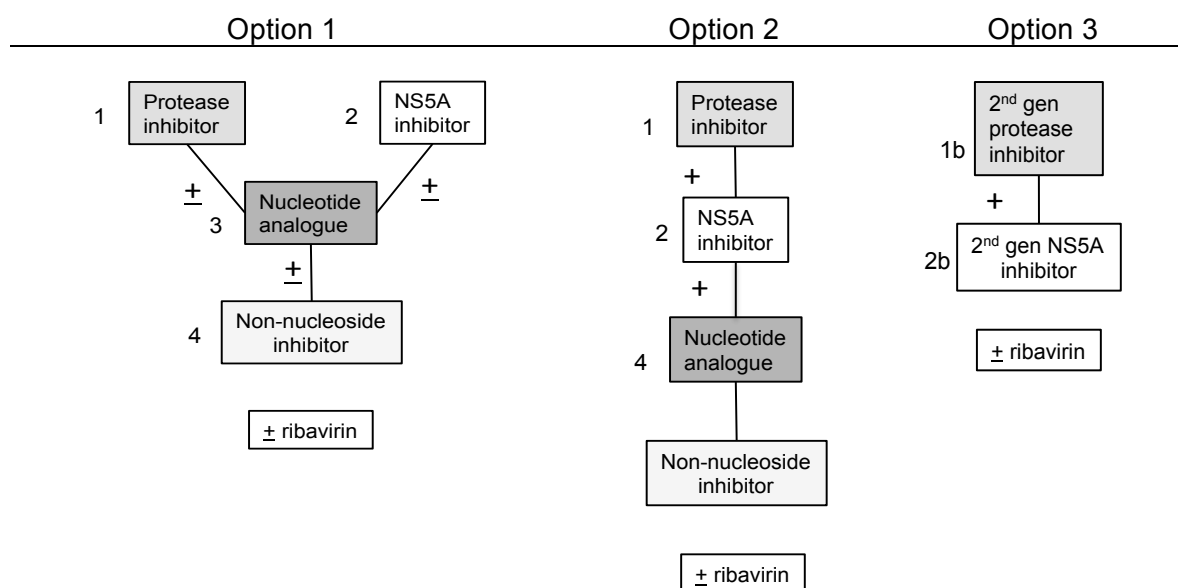
- ❖ Option #5: Sofosbuvir and daclatasvir – ALLY-1, 2 trials
  - Combination of daily sofosbuvir (400 mg) and daily daclatasvir (60 mg) (B2).
  - Treatment-naïve patients with or without cirrhosis 12 weeks without ribavirin (B2).
  - Treatment-experienced patients with or without compensated cirrhosis, 12 weeks with daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or ≥75 kg, respectively) (B2).
  - In treatment-experienced patients with or without compensated cirrhosis with contraindications to the use of ribavirin, extend to 24 weeks (B2).
- ❖ Option #6: Sofosbuvir and simeprevir
  - Combination of daily sofosbuvir (400 mg) and daily simeprevir (150 mg) (A1).
  - Treatment-naïve patients with or without cirrhosis 12 weeks without ribavirin (A1).
  - Treatment-experienced patients with or without compensated cirrhosis 12 weeks with daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or ≥75 kg, respectively) (B1).
  - In treatment-experienced patients with or without compensated cirrhosis with contraindications to the use of ribavirin, extend to 24 weeks (C1).

### **Genotype 5 or 6**

- ❖ Option #1: Sofosbuvir / ledipasvir
  - Fixed-dose combination of sofosbuvir (400 mg) and ledipasvir (90 mg) in a single tablet administered once daily (A1).
  - Treatment-naïve patients with or without compensated cirrhosis 12 weeks without ribavirin (B1).
  - Treatment-experienced patients with or without compensated cirrhosis 12 weeks with daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or ≥75 kg, respectively) (B1).
  - Treatment-experienced patients with or without compensated cirrhosis with contraindications to the use of ribavirin or with poor tolerance to ribavirin on treatment 24 weeks without ribavirin (B1).
- ❖ Option #2: Sofosbuvir / velpatasvir
  - Fixed-dose combination of sofosbuvir (400 mg) and velpatasvir (100 mg) in a single tablet administered once daily (A1).
  - Treatment-naïve and treatment-experienced patients with or without compensated cirrhosis 12 weeks without ribavirin (A1).
- ❖ Option #3: Sofosbuvir and daclatasvir
  - Combination of daily sofosbuvir (400 mg) and daily daclatasvir (60 mg) (B1).
  - Treatment-naïve patients with or without cirrhosis 12 weeks without ribavirin (B2).



- Treatment-experienced patients with or without compensated cirrhosis 12 weeks with daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or ≥75 kg, respectively) (B2).
- In treatment-experienced patients with or without compensated cirrhosis with contraindications to the use of ribavirin, extend to 24 (B2).
- Treatment-naïve
  - No cirrhosis
  - With Cirrhosis
  - With / without cirrhosis
- Treatment experienced
  - No cirrhosis
  - With Cirrhosis
  - Treatment failures



Adapted from: Pantolotsky JM. Gastroenterology 2015; 148: 468-479

- Special HCV treatment groups
- ❖ Acute Hepatitis C Infection
  - Treatment of acute HCV infection is recommended to ↓ risk of development of chronic HCV (~80%)
    - Genotypes 1, 4, 5 and 6 and HIV + HCV (HCV > 6.0 log IU/mL)
      - SOF + LED
      - SOF + VEL
      - SOF + DAC
  - HCV exposure
    - If no HCV transmission → No need for post-exposure prophylaxis
- ❖ Associated Immune Complex Disease
  - Systemic vasculitis
  - Mixed cryoglobulinemia



- ❖ B-cell non-Hodgkin lymphoma diffuse large B cell lymphoma
  - R-CHOP
  - Rituximab
- ❖ Bleeding disorders
  - HCV treatment is the same as for persons without bleeding disorders
  - Give factor VIII / IX concentrate just pre- and post-liver transplantation for 12-48 hr

#### Treatment Tip

- In the patient with HCV plus HIV, who also has hemophilia; consult drug-drug profiles carefully to choose the appropriate the therapeutic regime.

- ❖ HBV co-infection with HCV
  - Treat each using the same recommendations as either infection alone (i.e., monoinfected)
- ❖ Hemoglobinopathies
  - HCV treatment is the same as for persons without hemoglobinopathies, except
    - If RIB must be used, monitor and give packed red blood cells (PRBC) as indicated for anemia.
- ❖ People who inject drugs (PWID; aka intravenous drug users [IVDU]; drug addicts)
  - Test for anti-HCV, and if initially negative, then retest q1yr until anti-HCV becomes positive
  - Provide clean needles, safe injection sites, pre-treatment education, counselling and social service / peer support, methadone / buprenorphine substitution programs; multidisciplinary approach
  - Life style
    - Minimal / no intake of alcohol, cannabis
- Give factors which in the PWID patient with HCV is associated with ↓ SVR on anti-HCV medications.
  - Alcohol
  - Continued IVDU
  - Social / psychiatric issues

#### Treatment Awareness

- Where indicated, liver transplantation is appropriate in PWID-associated HCV disease, and opioid substitution is continued.

#### ❖ Renal Disease

- Glomerulonephritis – type 1 membranoproliferative
- Focal segmented glomerulosclerosis
- Interstitial nephritis

- Pharmaceutical
  - Anti-HCV therapy
  - Rituximab
  - Corticosteroid
  - Cyclophosphamide





- Genotypes 3
  - SOF + VEL
  - SOF + DAC

➤ **Monitoring during Treatment** (Assessment of Treatment Efficacy)

- When using INF-free anti-HCV regimen (DAA's), perform monitoring of adverse effects, plus laboratory measurements
  - Time 0 (baseline), 2 and 4 wk, then
  - At end of treatment, then
  - 12 (SVR<sub>12</sub>) or 24 (SVR<sub>24</sub>) weeks off treatment, i.e., after the end of treatment
- Laboratory
  - HCV RNA
  - HCV core antigen
  - CBC, ALT, Cr<sub>s</sub>, unconjugated bilirubin (if on simeprevir [SIM]), RIT + PAR + OMB + DAS

Laboratory Pearls

- If ↑ ALT while on DAAs, measure HBV DNA or HBsAg.

Treatment Gems

- With hepatic decomposition (C-P B/C), do not use protease inhibitors.
- RIB plus ↓ Hg < 10 g/dL
  - ↓ RIB doses by 200 mg
  - ↓ Hg < 8.5 g/dL
    - Stop the RIB
  - ↑ ALT > 10x ULN
    - Stop treatment
- HCV infected women who are of “child bearing potential” or +/- their male sexual partners should use an effective form of contraceptive during and for 6 mon after completement of any regimen which contains ribavirin.

Abbreviations: Cr<sub>s</sub>, serum creatinine concentration; DAAs, direct acting agents; eGFR, estimated glomerular filtration rate; Hg, hemoglobin concentration; SVR<sub>12</sub>/SVR<sub>24</sub>, sustained viral response at 12 or 24 wks; ULN, upper limit of normal

- Monitoring of drug-drug interactions
  - The efficacy and toxicity of concurrent drugs given for comorbidities and potential drug-drug interactions should be monitored during treatment.
  - When possible, an interacting co-medication should be stopped for the duration of HCV treatment or the interacting co-medication should be switched to an alternative drug with less interaction potential.

➤ **Post-liver transplantation recurrence**

- All patients with post-transplant recurrence of HCV infection should be considered for therapy.





- Treatment initiated early after liver transplantation
  - Ideally as early as possible when the patient is stabilized (generally after the first 3 months post-transplant), because the SVR<sub>12</sub> rates diminish in patients with advanced post-transplant liver disease.
- Acute cholestatic hepatitis or the presence of moderate to extensive fibrosis or portal hypertension one year after transplantation predict rapid disease progression and graft loss and indicate urgent antiviral treatment.
- Patients with post-transplant recurrence of HCV 1, 4, 5 or 6 genotype infection without cirrhosis (F0-F3), with compensated (Child-Pugh A) cirrhosis or with decompensated (Child-Pugh B or C) cirrhosis should be treated with
  - Fixed-dose combination of sofosbuvir and ledipasvir
  - Combination of sofosbuvir and daclatasvir for 12 weeks with daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or ≥75 kg, respectively)
  - Without immunosuppressant drug dose adjustments (with the probable exception of everolimus).
- Patients with post-transplant recurrence of HCV 2 genotype without cirrhosis (F0-F3), with compensated (Child-Pugh A) cirrhosis or with decompensated (Child-Pugh B or C) cirrhosis should be treated with
  - Sofosbuvir and daclatasvir for 12 weeks with daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or ≥75 kg, respectively)
  - Without the need for immunosuppressant drug dose adjustments (with the probable exception of everolimus).
- Patients with post-transplant recurrence of HCV 3 genotype should be treated with
  - Sofosbuvir and daclatasvir for 24 weeks regardless of the stage of liver disease, with daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or ≥75 kg, respectively)
  - Without the need for immunosuppressant drug dose adjustments (with the probable exception of everolimus).
- In the future, patients with post-transplant recurrence of all HCV genotypes without cirrhosis (F0-F3), with compensated (Child-Pugh A) cirrhosis or with decompensated (Child-Pugh B or C) cirrhosis could be treated with
  - Sofosbuvir and velpatasvir for 12 weeks (24 weeks in patients with genotype 3 and decompensated (Child-Pugh B or C) cirrhosis) with daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or ≥75 kg, respectively).
  - If / when the results of ongoing studies, particularly drug-drug interactions with immunosuppressant drugs, are found to be beneficial.

#### ❖ Ribavirin

- In patients with decompensated cirrhosis, ribavirin can be started at the dose of 600 mg daily and the dose subsequently adjusted depending on tolerance.
- Patients with contraindications to the use of ribavirin or with poor tolerance to ribavirin
  - Give the fixed-dose combination of sofosbuvir and ledipasvir (genotypes 1, 4, 5 or 6)
  - The fixed-dose combination of sofosbuvir and velpatasvir (all genotypes), or
  - The combination of sofosbuvir and daclatasvir (all genotypes) for 24 weeks without ribavirin.



## ❖ Sustained Virological Response (SVR) Obtained

- Non-cirrhotic with SVR
  - Cirrhotic with SVR (or F3 fibrosis)
- } – Treat to ↓ risks from diabetes, obesity, metabolic syndrome
- } – Continue HCV treatment if continued IVDU or MSM, but monitor for reinfection with HCV

Abbreviations: EGD, esophagogastroduodenoscopy; EV, esophageal varices; IVDU, intravenous drug use; MSM, men who have sex with men; SBP, spontaneous bacterial peritonitis; SVR, sustained virological response; ULN, upper limit of normal

## ❖ Non-sustained Virological Response

## ❖ Failure after a DAA-regimen

- METAVIR score F0 to F2
  - Retreat with same DAA regimen plus RIB for 12 wk
- F3 / cirrhosis
  - Same DAA regimen plus RIB for 24 wk

❖ Failure after SOF, SOF + RIB, or SOF + peg IFN- $\alpha$  and RIB

- Genotypes 1, 4, 5, 6 – SOF + LED
- All genotypes – SOF + VEL
- SOF + DAC
- Genotype 1 – RIT + PAR + OMB + DAS
- Genotype 4 – RIT + PAR + OMB
- SOF + SIM
- Genotypes 1 and 4 – ERA + ELB

## ❖ Failure after SOF / SIM

- Genotype 1 or 4
  - SOF + LED
  - SOF + VEL
  - SOF + DAC

## ❖ Failure after LED, VEL, OMB, ELB, DAC

- Genotype 1 – SOF + RIT + PAR + OMB + DAS
  - Genotype 4 – SOF + RIT + PAR + OMB
  - Genotype 1 or 4 – SOF + GRA + ELB
  - or
  - SOF + SIM + DAC
- 1a for 24 wk
  - 1b or 4, METAVIR F0 to F2 for 12 wk
  - 1b or 4, METAVIR F3 / cirrhosis plus RIB

## ❖ Failure after LED, VEL, or DAC

- Genotypes 2, 3, 5 or 6 – SOF + VEL + RIB for 24 wk

Note: Perform regular follow-up with serology, transient elastography (TE; Fibroscan®), and abdominal ultrasound q 6-12 mon



## DRUG-INDUCED LIVER INJURY (DILI): ACG GUIDELINES

Abbreviations: ACG, American College of Gastroenterology

Chalasani NP, et al. Am J Gastroenterol 2014; 109(7):950-66.

### ➤ Definition

- Intrinsic or idiosyncratic hepatocellular, cholestatic or mild toxicity to the liver, usually occurring within the first 6 mon after starting a new medication on herbal and dietary supplements (HDS)

### ➤ Demography

- Accounts for <1% of cases of acute liver injury

### ➤ Risk factors

- Gender has no effect on the risk of DILI
- Diabetes mellitus (DM) may ↑ severity (not risk) (OR 2.69, 95% CI 1.14 - 6.45)
- Heavy consumption
  - Acetaminophen
  - Isoniazid (INH)
  - Methotrexate
- Class effect
- Cross-sensitization
- Drug-interactions
- Polypharmacy
- Causality assessment
  - RUCAM score

### ❖ Roussel Uclaf Causality Assessment Method (RUCAM) Score

- Patient
  - Age
  - Alcohol use
  - Other drugs
  - Other liver conditions
- Liver response
  - Hepatocellular, cholestatic or mixed
- Drug
  - Start, stop
  - Initial, subsequent exposure
  - Other drugs
  - Drug predict information
  - Rechallenge



| Likelihood of DILI  | RUCAM score |
|---------------------|-------------|
| - Excluded          | $\leq 0$    |
| - Unlikely          | 1-2         |
| - Possible          | 3-5         |
| - Preferable        | 6-8         |
| - Highly preferable | $> 8$       |

Note: RUCAM score is only on "...adjunct to clinical impression" (Chalasani NP, et al. Am J Gastroenterol 2014; 109(7):950-66).

### ➤ Mortality

- 90% recover
- If acute liver failure (ALF) develops, it usually does so within 6 mon
- Time from development of jaundice to coagulopathy and hepatic encephalopathy ~ 2 wk
- High mortality for ALF in DILI
  - 6% death, or liver transplantation; more severe (9%) if hepatocellular

### SO YOU WANT TO BE A HEPATOLOGIST!

- In the context of DILI, give the meaning of Hg law.
  - During a phase 3 clinical trial, if a drug causes hepatocellular injury (ALT/AST  $> 3x$  ULN; bilirubin  $> 2x$  ULN when AP initially normal, and other causes of liver disease has been excluded, the mortality rate of this DILI is 10%
  - Acetaminophen toxicity leading to LF has a higher survival (70% vs 58%), LT-free survival (63% vs 23%) and lower need for LT (9% vs 40%)
  - In acetaminophen toxicity, survival rate is best predicted with the Sequential Organ Failure Assessment (SOFA)

|                              | DILI + ALF | DILI (acetaminophen) + ALF |        |     |
|------------------------------|------------|----------------------------|--------|-----|
| - Liver transplantation (LT) | 40%        | 9%                         |        |     |
| - LT-free survival           | 23%        | 63%                        |        |     |
| - Short term survival        | 58%        | 70%                        | NAC    | 58% |
|                              |            |                            | No NAC | 27% |

### ➤ Subtypes

|                                                           | Intrinsic | Extrinsic |
|-----------------------------------------------------------|-----------|-----------|
| ○ Affects all persons                                     | +         | -         |
| ○ Dose-dependent                                          | +         | -         |
| ○ Stereotype, variability (latency, presentation, course) | Low       | High      |



## ➤ Clinical

- When offending drug is stopped, improvement is used
  - Hepatocellular type
  - Cholestatic type

} 50% fall  
 - ALT, 30 - 60 d  
 - AP, 180 d

## ➤ Laboratory

R value = (ALT \* Upper Limit of Normal Alk Phos) / (Alk Phos x Upper Limit of Normal ALT)

## ○ Types

|                  | R value |
|------------------|---------|
| - Hepatocellular | ≥ 5     |
| - Mixed          | 2 – 5   |
| - Cholestatic    | < 2     |

Abbreviations: ALT, alanine aminotransferase; AP, alkaline phosphatase; ULN, upper limit of normal

## ➤ Differential

- Immune - Autoimmune hepatitis (AIH)
- Metabolic - Wilson disease
- Vascular - Budd-Chiari syndrome

| Group I               | Group II      |
|-----------------------|---------------|
| ○ HAV, HBV, HCV       | CMV, EBV, HSZ |
| ○ Alcohol             |               |
| ○ Biliary obstruction |               |
| ○ Shock liver         |               |

## ➤ Histopathology

- DILI may mimic range of hepatocellular and cholestatic disorders
- Liver biopsy indicated if another diagnosis besides DILI is suspected (e.g., AIH)
  - Liver enzyme (LEs)
  - Low RUCAM score (0-2)
  - Roenigk classification system for possible methotrexate-associated steatosis and fibrosis

## MCQ Tip

- Give the histological features on liver biopsy which suggest a good prognosis in DILI.
  - ↑ eosinophils
  - ↓ necrosis

} ↑ likelihood of recovery

Please also see Seeff LB, et al. Herbal Products and the Liver. Gastroenterology 2015; 148: 517-532.



## COMPLICATIONS OF LIVER DISEASE

### EVALUATION OF ABNORMAL LIVER CHEMISTRIES: ACG GUIDELINE

Abbreviations: ACG, American College of Gastroenterology

Kwo PY, et al. Am J Gastroenterol 2017; 112: 18-35.

#### ❖ Bilirubin

- Fractionation of total bilirubin is helpful when levels of ALT, AST, AP are normal / near normal
- ↑ conjugated (direct)
- ↑ unconjugated (indirect)
  - Hemolysis, ↓ hepatic obstruction
- ↑ conjugated bilirubin
  - Hepatocellular or cholestatic liver disease and delta bilirubin (reaction of conjugated bilirubin with albumin)
- The half-life of albumin is 3 wk
- “Isolated unconjugated / indirect hyperbilirubinemia” usually mild (< 5 mg/dL), unless
  - Severe acute hemolysis
  - Associated hepatic or renal disease

#### ❖ INR

- INR measures extrinsic pathway of coagulation related to clotting factors 1, 2, 5, 7, 9 (vitamin K dependent 2, 7, 9, 10)
  - Clotting factors ↓ by 90% before INR ↓

### SO YOU WANT TO BE A GASTROENTEROLOGIST!

- Give conditions which result in an ↑ INR.
  - Drugs
    - Warfarin
    - Heparin (bolus)
  - Disseminated intravascular coagulation (DIC)
  - Hypothermia

#### ❖ Transaminases (ALT, AST)

- New upper limits of normal (ULN)
- ALT / AST > ULN
  - ↑ all cause mortality (3x)
  - ↑ liver-related mortality (29x)
  - ↑ diabetes-related mortality (3x)
- ALT > AST (liver bigger than spleen), except with ALD, NAFLD, fibrosis



- Give the liver-disease related causes of ALT / AST > 1000 IU/L.
  - Shock liver
  - Autoimmune
  - Infection (A-E, CMV, HSV, EBV)
  - DILI
- ❖ Alkaline phosphatase (AP)
  - ↑ synthesis by canalicular cells with cholestasis
  - ↑ AP plus bile ducts
    - Dilation                      extrahepatic disease
    - No dilation                  intrahepatic disease
  - α-1 anti-trypsin deficiency (α1ATD)
    - ↑ AST / ALT persistently
      - ↓ alpha-1 antitrypsin
      - Genotype
        - PiZZ
        - PiMZ, especially of associated viral hepatitis or NAFLD
  - Primary sclerosing cholangitis (PSC)
    - ↑ anti-neutrophil cytoplasmic antibody
    - ↑ IgG
    - ↑ IgG4 (IgG4-associated PSC)
- Give the approximate prevalence of hereditary liver conditions seen in adults.

| Disease                      | Prevalence, per 10 <sup>5</sup> |
|------------------------------|---------------------------------|
| ○ Hereditary hemochromatosis | 400                             |
| ○ α-1 antitrypsin deficiency | 40                              |
| ○ Wilson disease             | 30                              |

In hepatocellular and in cholestatic disease both the transaminases and the alkaline phosphatase may both be elevated (mixed picture).

- Give the way to determine what is predominant pattern (hepatocellular or cholestatic disease).
  - Whichever test is disproportionally elevated (i.e., when one has the greatest increase divided by the ULN)
  - R ratio (ALT value in patient / ALT ULN) + (AP value in patient / AP ULN)
    - R > 5 hepatocellular disease; R < 2, cholestatic disease



\* Specific Conditions

- Alcoholic liver disease (ALD)
  - Gram of alcohol intake per wk
    - Men > 210
    - Women > 140
  - $\uparrow$  AST / ALT usually < 300 IU/L
  - AST > ALT, AST / ALT > 2 – 1 to 3 – 1
  - $\uparrow$  ALT, AST and GGT suggest ALD
  - $\uparrow$  GGT in 50% of alcoholic patients without liver disease
- Autoimmune liver disease (ALD)
  - Serology
    - Anti-nuclear antibody (ANA)
    - Anti-smooth muscle antibody (ASMA)
    - Anti-liver kidney microsomal antibody (ALKMA)
    - Anti-soluble liver antigen antibody (ASLAA)
    - $\uparrow$  IgG (IgA  $\uparrow$  in ALD, IgM  $\uparrow$  in PBC)
- HCV
  - HC antibody +  $\rightarrow$  confirm with HCV RNA PCR assay (<http://www.hcv.org/full-report/hcv-testing-and-linkage-care>)
  - Universal testing recommended for birth cohort 1945 – 1965
  - ALT may be normal in HCV despite active inflammation
- HBV
  - HBsAg
    - Infection
  - HBsAb
    - Immunity
  - HBeAb
    - Prior exposure
  - HBc antibody IgM
  - HBV DNA
  - HB genotype
  - HB viral load
- Hereditary Hemochromatosis (HH)
  - Screen when  $\uparrow$  ALT /  $\uparrow$  AST persistently
  - Suspect when TS > 45%, ferritin > 1000  $\mu$ g/L
  - Homozygous C282Y have HH, but may not develop phenotype with iron overload





## HEPATOVENOUS PRESSURE GRADIENT (HVPG)

- Normal values
  - WHVP (mm Hg) (SP)
  - FHVP
  - HVPG 3-5 mm Hg
  - Sinusoid hypertension HVPG > 5 mm Hg
  - Mild PH      HVPG > 5 but < 10 mm Hg
  - CSPH        HVPG > 10 mm Hg
- EGV develop when HVPG > 10 mm Hg
  - HV from EGV occurs when HVPG > 12 mm Hg
  - When HVPG > 16 mm Hg
    - Each 1 mm Hg increase in HVPG predicts a 3% ↑ risk of death over 19 mon
  - Failure to control bleeding from acute VH
    - Early rebleeding
    - Death from acute VH

Abbreviations: CSPH, clinically significant portal hypertension; EGV, gastroesophageal varices; FHVP, free hepatic venous pressure; HVPG, hepatic vein pressure gradient; PH, portal hypertension; VH, variceal hemorrhage WHVP, wedge hepatic venous pressure

- Give the use of measurements in the hepatic vein (HV) to determine the site of ↑ resistance to blood flow and thus to classify the type of portal hypertension.
  - WHVP = FHVP > normal
    - Prehepatic (PVT, portal vein thrombosis)
    - Presinusoidal
      - Cholestatic cirrhosis
      - IPT (idiopathic portal hypertension)
      - Schistosomiasis
  - ↑ WHVP, ↑ FHVP, normal HVPG
    - Right-sided heart failure (R-HF)
  - ↑ WHVP, ↑ HVPG (FHVP normal)
    - Sinusoidal
      - Cirrhosis
    - Post-sinusoidal
      - SOS (sinusoidal obstruction syndrome)

### Trick MCQ

- Give the anticipated values of WHVP, FHVP and HVPG in patients with Budd-Chiari syndrome (BCS).
  - In BCS, there is obstruction of the hepatic vein, so it is not possible to measure WHVP, FHVP, or to calculate HVPG.



➤ Diagnosis

❖ CSPH (clinically significant portal hypertension)

- Give the methods to diagnose clinically significant portal hypertension (CSPH, HVP  $\geq 10$  mm Hg) without measurements of hepatic vein pressure (WHVP, FHVP, HVP).
- Physical examination
  - Spider nevi
  - Portosystemic collaterals (e.g., caput medusae)

Clinical Gem

- Remember the lack of these physical findings does not rule out CSPH

- Laboratory
  - Platelet count  $< 150,000/\text{mm}^3$  plus 1 ultrasound abnormalities suggesting  $\uparrow$  likelihood of CSPH
    - Please see ISPS below
- Diagnostic imaging ( $\geq 99\%$  specific for CSPH)
  - US, CT, Doppler ultrasound
    - Portal vein (PV)
      - $\downarrow$  flow velocity
      - Dilated
      - Abnormal congestion index
      - Retrograde flow
    - Portocollateral circulation
  - MRI
    - Paraumbilical vein recanalized
    - Splenorenal
      - Spontaneous circulation
    - Left / short gastric veins
      - Dilated
    - Spleen
      - $\uparrow$  size in cirrhosis / PHT
      - $\uparrow$  spleen stiffness (SS) by TE (can be measured only if spleen enlarged)

Trick MCQ

- Give the measurement which may best predict the first clinical decompensation of the cirrhotic liver.
  - Spleen stiffness (SS)  $> 54$  kPa by transient elastography (TE) is similar to measurement of HVP and is better than liver stiffness by TE to predict imminent decompensation
  - In another study, prediction of decompensation was equivalent for HVP  $\geq 10$  mm Hg (CSPH) and for LS  $\geq 21$  kPa



- Stiffness
    - Transient elastography (TE)
    - Liver stiffness (LS)
      - > 20-25 kPa (kilopascals) has a diagnostic accuracy of >90% of for CSPH
    - Spleen stiffness (SS)
      - Sonoelastographic shear wave elastography (SWE)
      - Specificity ~90%
      - Positive predictive value (PPV) > 90%
- } Ruling in the diagnosis of CSPH
- Combination of LS x spleen size / platelet count > 206 (LSPS): please see next section for use to rule out high risk GEV (likely to bleed)
  - LS determined by MRE (under development)

#### ❖ CSPH

- Clinically significant portal hypertension (CSPH) may be established
  - Invasive tests
    - GEV on EGD
    - HVP  $\geq 10$  mm Hg, or by
  - Non-invasive tests
    - Liver stiffness (LS) by TE > 20-25 kPa, +/-  $\downarrow$  platelet count and  $\uparrow$  spleen size
    - Diagnostic imaging showing portosystemic collaterals

#### ❖ Endoscopic (EGD) surveillance for development of new GEV, or enlargement of previous GEV with development of high risk features for variceal hemorrhage (VH)

- Compensated cirrhosis (CC)

|                                         | Frequency of Endoscopic<br>Surveillance, yrs |
|-----------------------------------------|----------------------------------------------|
| - No varices / varices on screening EGD |                                              |
| ▪ Ongoing injury +/- obesity, alcohol   | 2                                            |
| ▪ No ongoing injury                     | 3                                            |
| - Small varices on screening EGD        |                                              |
| ▪ Ongoing injury +/- obesity, alcohol   | 1                                            |
| ▪ No ongoing injury                     | 2                                            |

Trick MCQ: By how much must prophylactic therapy (NSBB) reduce HVP?

- HVP
  - > 10 GEV form
  - > 12 GEV  $\rightarrow$  VH
- 10%  $\downarrow$  baseline of HVP in CC
  - $\downarrow$  development of GEV
  - $\downarrow$  first VH
  - $\downarrow$  mortality rate



- Under development response to IV propranolol 0.15 mg/kg may predict long-term outcome of primary prophylaxis with NSBB without
- 20% ↓ baseline of HVPG in compensated cirrhosis (CC)
  - ↓ recurrent VH
  - ↓ ascites / ↓ HE
  - ↓ mortality rate
- Non-invasive tests (NIT) for gastroesophageal varices (GEV)
  - Platelet count  $> 150,000 / \text{mm}^3$  plus LS  $< 20$  kPa by TE
  - $< 5\%$  risk if presence of high risk GEV
- Liver stiffness x spleen size / platelet count (LSPS)  $< 3.5$ 
  - Rule out high-risk varices

#### MCQ Trick

- These non-invasive tests for high-risk gastroesophageal varices (GEV) may ↓ requirement for EGD surveillance of GEV presence, size and other risk factors for varice hemorrhage (VH).

#### ❖ GEV / VH

- Liver stiffness (LS) TE  $< 20$  kPa plus platelet count  $> 150,000 / \text{mm}^3$  predict or have  $< 5\%$  probability of the presence of high-risk GEV which are likely to be VH
  - Screening EGD can be avoided
- LS  $> 20$  kPa and platelets  $< 150,000 / \text{mm}^3$  need screening EGD for GEV when diagnosis of cirrhosis is made
- Compensated cirrhosis (CC)
  - In CC, screening EGD
    - No GEV
      - Repeat EGD
        - In 2 yr of ongoing hepatic injury +/- obesity, alcohol use
        - 3 yr of no ongoing hepatic injury, alcohol use
    - Small GEV
      - Repeat EGD
        - In 1 yr of ongoing hepatic injury, alcohol use
        - In 2 yr of no ongoing injury, no alcohol use
  - When decompensated develops
    - No GEV or small GEV
    - Immediately repeat EGD upon development of GEV
  - In clinical practice (outside clinical trials) do not monitor HVPG or perform non-invasive tests for HVPG

#### ➤ Treatment

#### ❖ Goals of therapy

“...these complications...should be considered in the context of advances in the staging of cirrhosis and in the context of other complications of cirrhosis that may occur concomitant or subsequent to development of venous and variceal hemorrhage [VH].” (Garcia-Tsao G, et al. Hepatology 2017; 65: 310-335)



### Stratify risk by stage / substage of cirrhosis

- Compensated
  - Mild portal hypertension (PH)
  - CSPH (clinically significant PH)
    - GEV
      - No
      - Yes
- Decompensated
  - VH, HE, ascites
  - Note: Distinction between presence of varices (GEV), and hemorrhage from variceal (VH)

Abbreviations: GEV, gastroesophageal varices; HE, hepatic encephalopathy; PH, portal hypertension

- Give why the use of alcohol and obesity are important therapeutic factors for all patients with cirrhosis, independent of etiology.
    - Alcohol
      - ↑PP / ↑PH
      - ↓ prognosis of HCV / NASH cirrhosis
    - Obesity
      - ↑ fibrosis
      - ↑ decomposition
      - ↓ regression (viral cirrhosis)
    - Decompensated cirrhosis
      - HVWP  $\geq$  12 mm Hg
      - Complications
        - VH
        - HE
        - Ascites
      - Goals of therapy
        - Avoid alcohol / obesity
        - Treat acute VH
        - Prevent GEV progression, further VH
        - Treat / prevent HE, ascites, SBP, HRS, HCC
  - Compensated cirrhosis (CC) plus mild PH (HVPG > 5 but < 10 mm Hg)
    - Possibility for stopping progression to CSPH, or causing regression of cirrhosis
      - Fibrosis septa still thin and fibrogenesis is possible regression of hepatic
    - Statins
      - Mechanisms of action in this setting
        - ↓ hepatic fibrogenesis
        - ↓ portal pressure
          - ↓ decompensation
          - ↓ mortality
- } Shown in HCV compensated cirrhosis



MCQ Trick: How to identify this group of patients

- In patients with no gastroesophageal varices (GEV), the only way to disprove the presence of CSPH and to prove CC plus mild PH is to measure HVPg (to prove HVPg > 5 but < 10 mm Hg)

Abbreviations: CC, compensated cirrhosis; CSPH, clinically significant portal hypertension; GEV, gastroesophageal varices; HVPg, hepatic venous pressure gradient

❖ CC plus mild PH

- Treat the etiology of the underlying liver disease
- Treat associated obesity/alcohol abuse
- Follow the literature and advice patient about potential benefit of statins

- CC plus CSPH (HVPg  $\geq$  10 mm Hg)
  - NSBB do not prevent the development of GEV

SO YOU WANT TO BE A HEPATOLOGIST!

- Give the criticism of the clinical study which failed to show a response to the NSBB “timolol” in the primary prevention of GEV.
  - The patient group had compensated cirrhosis, but within this cohort there were two subgroups
    - CC plus mild PH
    - CC plus CSPH

Greater in CSPH

- These groups are different in terms of
 

|                                        |   |
|----------------------------------------|---|
| – HVPg                                 | + |
| – Presence of hyperdynamic circulation | + |
| – Quantitative response to NSAIDs      | + |

❖ CC plus CSPH but no GEV

- Follow same suggestions as for CC plus mild PH to ↓ risk of progression (decompensation: GEV)



### MCQ Pearl

Hemodynamic responders to NSBB have ↓ VH, ↓ decompensation, ↓ mortality

- ❖ CC plus CSPH with GEV (HVPg 10-12 mm Hg)
  - To prevent variceal hemorrhage (VH) in this CC plus CSPH group with GEV, the treatment objective is to
    - ↓ HVPg to  $\leq 12$  mm Hg, or
    - ↓ HVPg > 20% from baseline
  - However, the guidelines of adjusting the dose of NSBB to ↓ heart rate (HR)  $\leq 55$  bpm or 20% ↓ of HR from baseline is a questionable benefit, because changes in HR do not correlate closely with HVPg.
  - Therefore, in patients with CC plus GEV, NSBB are given to patients with GEV that are at high risk of VH.
    - High risk GEV
      - Size medium / large GEV
      - Red wale sign
      - Decompensated cirrhosis

### Note

- In this setting
  - NSBB have several benefits
    - ↓ first VH (primary prophylaxis)
    - ↓ ascites
    - ↓ death
  - Endoscopic variceal ligation (EVL)
    - ↓ VH (EBV > NSBB)
    - ↓ mortality (EBL = NSBB)
    - Repeat q 2-8 wk with GEV, are eradicated, then repeat EGD at 3-6 mon after eradication, then every 6-12 mon

### MCQ Gem

Once a patient is on NSBBs for prophylaxis of VH, EGD does not need to be repeated.

- ❖ CC plus CSPH plus medium/large GEV
    - NSBB, carvedilol or EVL → q 2-8 wk until eradication, then 3-6 mon later, then q 6-12 mon long-term
    - Tips for primary prophylaxis (prevention of first VH) not recommended
- Note: NSBB, carvedilol: EGD monitoring not necessary

Abbreviations: CC, compensated cirrhosis; CSPH, clinically significant portal hypertension; EGD, esophagogastroduodenoscopy; NSBB, non-specific beta blocker; TIPS, transjugular intrahepatic portosystemic shunt



## ❖ Medium / large GEV

## Therapeutic Tip

- Give the benefits of NSBB in patients with medium/large varices, in addition to other benefits of primary and secondary prophylaxis for VH.
  - “It depends”
    - In hemodynamic responders, there is
      - ↓ decompensations of the cirrhosis
      - ↓ mortality
  - Remember that only about 70% of cirrhotic patient who are eligible for NSBB can use the medication because 30% have
    - Contraindication (15%)
    - Adverse effects (15%)
  - But
    - In those who can take NSBB, there are advantages over EBL such as
      - No need to repeat EGD
      - Effective for complications of PH in addition to VH

Abbreviations: EBL, esophageal (varicella) band ligation; EGD, esophagogastroduodenoscopy; NSBB, non-specific beta blockers; PH, portal hypertension; VH, variceal hemorrhage

- Give the benefits of EVL + NSBB vs EVL alone.
  - None

## ❖ Primary prophylaxis

- Small esophageal varices (EV)
- NSBB for primary prophylaxis (prevent first bleed) for small EV with high-risk signs for future bleeding
  - Varices
    - Red wale marks +/-
  - Patient
    - CTP-C

## ❖ Medium/large GEV

- To prevent first VH
  - NSBB = EVL
  - Carvedilol ≥ EVL
- Primary prophylaxis (prevent first VH)
  - NSBB/carvedilol or EBL, depending on patients, characteristics, expertise, cost, contraindications
- Non-specific beta blocker (NSBB)
  - Primary prophylaxis
    - No need to repeat esophagogastroduodenoscopy (EGD)
- Transjugular intrahepatic portosystemic shunt (TIPS)
  - Not recommended





## ❖ Acute variceal hemorrhage (VH)

## • Early

- Risk of rebleeding
  - In first year, 60%
  - Mortality rate, 33%

## ➤ Prognosis

- Later (5-yr mortality rate)
- Isolated decompensation, 20%
- Decompensation with other complications (e.g., HE, ascites), 80%

## ➤ Risk stratification

- Since the HVPg is the best predictor of GEV early rebleeding (reVH), as well as death, but
  - HVPg measurements are less readily available
- Use the CTP class as a surrogate for HVPg

CTP class C > 80% have HVPg  $\geq$  20 mm Hg

## Therapeutic Reminder

- As soon as possible patient with acute VH is sufficiently stable, obtain abdominal ultrasound to determine if there is
  - Venous thrombosis
    - PV, HV, SV
  - Hepatocellular carcinoma (HCC)

Abbreviations: CTP, Child-Turcotte-Pugh; HE, hepatic encephalopathy; HV, hepatic vein; HVPg, hepatic venous pressure gradient; PV, portal vein; reVH, recurrent variceal hemorrhage; SV, splenic vein

## ➤ Outcome

- Control VH
- ↓ early recurrence of VH
- ↓ 6 wk mortality rate
- IV infusion of albumin / volume while awaiting pack red blood cells (PRBC)
  - Target hemoglobin concentration (Hg)
    - Begin PRBC transfusion at 7 g/dL
    - Maintain Hg between 7-9 g/dL



- Give the benefit of initiating PRBC infusion at 7 g/dL and maintaining the values between 7-9 g/dL.
  - ↓ risk of further increasing the HVPG and enhancing further variceal hemorrhage
  - ↓ early rebleeding of EV
  - ↓ mortality rate
  - Correcting coagulopathy
    - Do not use INR to estimate coagulopathy severity (in the cirrhotic patient the value of the INR reflects hepatic synthetic function, not the severity of coagulopathy).
      - Fresh frozen plasma (FFR) or factor VIIa
  - Platelet transfusion
  - Infection
    - All patients with cirrhosis and upper GI bleeding (UGIB, regardless of cause) require early antibiotic prophylaxis (before EGD)
      - Ceftriaxone IV 1 g stat and 1 g OD (daily, every 24 hr for 7 d)
  - Vasoactive agent
    - Octreotide (equivalent to somatostatin, and to terlipressin + vasopressin analog)
      - 50 mcg IV stat bolus, repeat within 1 hr if necessary, then 50 mcg/hr
  - Continue for 2-5 d, then immediately start NSBBs
  - Author's note
    - Commonest cause of UGIB in cirrhosis
      - Peptic ulcer disease
    - Most dangerous cause of UGIB in cirrhosis
      - Variceal bleeding
    - Proton pump inhibitors (PPIs) may be used
    - Pre-EGD in the cirrhotic patient with UGIB, give both PPIs and vasoactive agents (e.g., somatostatin)
  - Esophagogastroduodenoscopy (EGD) / EVL
    - Perform as soon as possible once bleeding peptic ulcer patient is hemodynamically stable, and within 12 hr of admission
    - Esophageal [variceal] band ligation for EV and 2 mode endoscopic therapy for bleeding gastric / duodenal ulcers

#### Clinical Tip

- How to be sure that the UGIB was due to VH in the patient with GEV?
  - Seeing a bleeding GEV
  - GEV with stigmata
    - White nipple
    - Red wale
  - No other lesion seen to account for the UGIB



In follow-up after discharge, use combination therapy of EVL + NSBB to ↓ risk of second bleed (secondary prophylaxis)

- Preemptive TIPS (within 72 hr)
  - Second rebleed
    - Modest → repeat EVL
    - Severe → consider TIPS
  - CTP-C with active VH despite vasoactive drugs (octreotide, somatostatin, vasopressin, terlipressin)
  - CTP-B with active VH despite vasoactive drugs
  - With rebleeding (VH) high risk of failure of EVL / AP, or continued VH
- Preemptive TIPS procedure within 72 hr in the ~ 20% of high risk cirrhotic will further decrease (high risk)
  - Rebleeding
  - Deaths
- Use “covered TIPS stent” (polytetrafluoroethylene covering) or placement of endoscopically placed self-expandable metal stents (SEMS)
- Assess for liver transplantation, Doppler ultrasound for TIPS patency q 6 mon
- Balloon tamponade
  - “bridge” to TIPS / liver transplantation
  - Use in only high-risk continuous EV
  - With rebleeding balloon tamponade for no more than 24 hr
  - SEMS
    - Superior to balloons for greater control of bleeding, and fewer complications
    - Keep in place for 7 d

#### Guidelines

- NSBB
  - Restart on day 2-5 when vasoactive agents are stopped.
- PRBC transfusion started at hemoglobin concentration (Hg) 7 g/dL, and maintained to keep Hg 7-9 g/dL
- Antibiotics ceftriaxone 1 g/d IV for 7 d
- Vasoactive drugs for 2-5 d
- EGD when patient is stable and within 12 h of admission for EVL of varices
- Early TIPS of high risk of continued VH, rebleeding despite vasoactive drugs + EVL
- Vasoactive drugs 2-5 days
  - Stop, and start NSBB
  - If TIPS placed, stop vasoactive drugs

Abbreviations: EGD, esophagogastroduodenoscopy; EVL, esophageal variceal ligation; NSBB; non-specific beta blockers; PRBC, packed red blood cells; TIPS, transjugular intrahepatic portosystemic shunt



## ❖ Precautions with use of NSAIDs

- Refractory ascites or previous SBP
  - Avoid use of high doses of NSBB
- Refractory ascites plus circulatory dysfunction\*
  - ↓ / temporary stop NSBB until circulatory dysfunction is improved
- Primary prophylaxis with NSBB
  - When VH occurs, VH may be more aggressive
    - ↑ rebleeding
    - ↑ mortality

} Consider earlier use of TIPS

\* Circulatory dysfunction

SBP < 90 mm Hg

$\text{Na}^+_s < 130 \text{ mEq/L}$

Hepatorenal syndrome (HRS)

Abbreviations:  $\text{Na}^+_s$ , serum sodium concentration; SBP, spontaneous bacterial peritonitis

## ❖ GEV, VH, and HCC

- Variceal hemorrhage (VH) may be more severe when there is HCC
  - The treatment of VH in the patient with HCC is the same as, and is as efficient as with patient with VH and no HCC.

## ❖ Maintenance after recovery from acute VH

- NSBB plus EVL
  - ↓ all cause of GI bleeding
  - ↓ trend to ↓ mortality
  - Carvedilol
    - “not enough data to recommend carvedilol in the presentation of rebleeding” if esophageal varices

} Rebleeding → TIPS (stop NSBB and repeat EGD)

## Therapeutic Tips

- Do not use carvedilol for primary prevention of HV in persons with refractory ascites

## ❖ Maintenance

- NSBB + EVL  $\xrightarrow{\text{rebleeding}}$  TIPS (covered stent) (rebleeding 0% vs 25% for EVL / glue injection)
- NSBB (hemodynamic responders); HVPG < 12 mm Hg / > 20% from baseline
  - Lowest rate of rebleeding
- Secondary prophylaxis (prevention of rebleeding)
  - Primary prophylaxis
    - NSBB + EVL  $\xrightarrow{\text{rebleeding}}$  TIPS
    - TIPS
      - No NSBB, no EVL
      - Early treatment for HE
      - Periodic abdominal ultrasound to detect portal vein thrombosis (PVT)



## ACUTE LIVER FAILURE: AASLD POSITION PAPER / AGAI GUIDELINES

Abbreviations: AASLD, American Association for the Study of Liver Disease; AGAI, American Gastrointestinal Association Institute

Flamm SL, et al. Gastroenterology 2017; 152: 644-647; and AASLD: Lee WM, et al. Hepatology 2011; 55: 1-22.

- Acute liver failure (ALF)
  - Hepatic encephalopathy, INR  $\geq 1.5$ , in a non-cirrhotic patient with a liver illness < 26 wk duration
  - Risk stratification

Modified King's College Criteria for Poor Prognosis in ALF.

- Clinical diagnosis of ALF
  - ↓
  - Test for
    - HSV and autoantibodies
    - Wilson disease if ↑ clinical suspicion
    - HEV in pregnant women
  - ↓
  - Treat for acetaminophen-associated ALF with NAC
  - Do not's
    - Routine
      - Testing for WD, VZV
      - Liver biopsy
      - Empiric ↓ of intracranial pressure (ICP)

In context of clinical trial

- NAC for non-acetaminophen ALF
- Extracorporeal artificial liver support

### Non-acetaminophen-induced

- INR > 6, 5 and any encephalopathy
- Bilirubin  $\geq 17$  mg/dL
- Unfavourable etiology
  - Wilson disease
  - DILI (idiosyncratic)
  - HBV infection
  - Mushroom poisoning
  - Budd-Chiari syndrome
  - Indeterminate etiology



**Acetaminophen-induced**

- INR > 6.5, HE 3 / 4
- pH < 7.3, or
- Arterial lactate > 3.0 - 3.5 mmol/L after fluid resuscitation
- Cr<sub>s</sub> > 3.4 mg/dL



- Admission to ICU, notification of liver transplantation centre
- Perform diagnostic tests to establish etiology
- Periodic surveillance cultures
- Give specific therapy for treatable causes of ALF



- 0.9% ("normal" saline) for fluid resuscitation and maintenance
- Volume
  - Refractory hypotension
  - Monitor and correct serum K<sup>+</sup>, Mg<sup>2+</sup>, phosphate, glucose
  - Norepinephrine
  - If norepinephrine-refractory hypotension, add vasopressin or terlipressin to maintain MAP ≥ 75 mmHg, CPP 60 - 90 mmHg
- Endotracheal intubation
- Bleeding
  - Prophylaxis for stress bleeding
  - H<sub>2</sub> receptor antagonists, or
  - Proton pump inhibitors
  - Bleeding from ↓ platelets or recent invasive procedures
  - Fresh frozen platelet (FFP) replacement
- Seizure
  - Phenytoin plus short half-life benzodiazepines
- Monitor renal function (Cr<sub>s</sub>)
- Intracranial pressure monitoring (ICP)
  - If no ICP available, hourly CNS exam



- ↑ ICP
  - Mannitol bolus 0.5 - 1.0 g/kg body weight
    - Serum NH<sub>3</sub> > 150 μm
    - HE grade 3 / 4
    - AKI
    - MAP maintained with vasopressors



- Hypertonic NaCl to target Na<sub>s</sub><sup>+</sup> 145 - 155 mEq/L



Refractory to osmotic agents



- Hypothermia (body core 34 - 35°C), plus short-acting barbiturates
- Lactulose, but not in doses to cause abdominal distention (may interfere with possible LT)



Manage associated causations of treatable ALF

❖ Associated treatable causations

- |                                            |                                                                  |                |
|--------------------------------------------|------------------------------------------------------------------|----------------|
| ○ Acetaminophen overdose                   | - Within 4 hr                                                    |                |
|                                            | ▪ Activated charcoal                                             |                |
|                                            | ▪ N-acetylcysteine (NAC)                                         |                |
| ○ Amanitor phalloids poisoning             | - NAC                                                            |                |
|                                            | - Penicillin G                                                   |                |
|                                            | - Silibin, if available                                          |                |
| ○ Possible DILI, herbs, dietary supplement | - Stop potentially offending agent                               |                |
| ○ HBV infection                            | - Nucleos(t)ide analogs                                          |                |
| ○ HSV, HZV infection                       | - Acyclovir                                                      |                |
| ○ Wilson disease                           | - Liver transplantation                                          |                |
| ○ Autoimmune hepatitis                     | - Corticosteroids, plus LT assessment                            |                |
| ○ AFLP, HELLP                              | - LT if mother does not improve quickly after delivering of baby |                |
| ○ Acute ischemic hepatic injury            | - Provide appropriate CV support                                 |                |
| ○ HV thrombosis (BCS)                      | - Assess for LT                                                  |                |
| ○ Possible malignant infiltration          | - Previous cancer diagnosis                                      | } Liver biopsy |
|                                            | - Massive hepatomegaly                                           |                |



❖ Liver transplantation

- CLT / LDLT when prognosis poor: Urgent hepatic transplantation is indicated in acute liver failure where prognostic indicators suggest a high likelihood of death
- However currently available prognostic scoring systems (e.g., King's College Criteria) do not adequately determine candidacy for liver transplantation"
- Reliance entirely upon the guidelines is thus not recommended

Abbreviations: AFLP, acute fatty liver of pregnancy; AKI, acute kidney injury; ALF, acute liver failure; BCS, Budd-Chiari syndrome; CPP, cerebral perfusion pressure; Cr<sub>s</sub>, serum concentration of creatinine CV, cardiovascular; DILI, drug-induced liver injury; FFP, fresh frozen plasma; HBV, hepatitis B virus; HELLP, hemolysis elevated liver enzymes low platelets; ICP, intracranial pressure; ICU, intensive care unit; LT, liver transplantation; NAC, N-acetyl cysteine; NaCl, sodium chloride; Na<sub>s</sub><sup>+</sup>, serum sodium concentration; NH<sub>3</sub>, serum ammonia



## HEPATIC ENCEPHALOPATHY (HE): AASLD AND EASL CLINICAL PRACTICE GUIDELINES

Abbreviations: AASLD, American Association for the Study of Liver Diseases; EASL, European Association for the Study of the Liver

Vilstrup H, et al. Hepatology 2014; 60: 715-735.

### ➤ Definition

- Multidimensional brain dysfunction occurring in the patient with liver insufficiency (and no other cause of brain dysfunction) and / or portosystemic shunting resulting in attention, behaviour, cognitive, memory and motor changes.

### ➤ Demography

- Hepatic encephalopathy, ascites and esophageal varices define the compensation phase of cirrhosis.
- HE occurs
  - At the time of diagnosis of
    - Cirrhosis ~15%
  - Within 5 yr of diagnosis of cirrhosis
    - Decompensation ~ 20%
    - At some time during the patients cirrhosis ~ 40%
  - After first episode of HE
    - Second episode occurs at 1 yr in 40%
    - Third episode occurs within 6 mon in 40%
- Hepatic encephalopathy affects 30% of patients with cirrhosis, and about the same percentage of cirrhotics admitted to hospital have an altered mental status.

### ➤ Classification

- HE underlying cause
  - A – Acute liver failure (ALF) → see Guidelines for ALF
  - B – Portosystemic shunting (PSS) or bypass
  - C – Cirrhosis
- Severity (continuum)
  - West Haven criteria
  - Glasgow Coma Scale (if ↓ LOC is present)
- Time course
  - Episodic
  - Recurrent (within ≤ 6 mon)
  - Persistent (with relapses)
  - Acute-on-chronic liver failure (ACLF)
- Precipitating factors
 

|           |                    |
|-----------|--------------------|
| - Absent  | ▪ Non-precipitated |
| - Present | ▪ Precipitated     |

ISHEN defines the onset of brain dysfunction in HE as the onset of disorientation or asterixis

### ➤ Terms

- Minimal hepatic encephalopathy (MHE)
  - Psychometric testing abnormal
- Covert hepatic encephalopathy (CHE)
  - MHE or grade I
- Overt hepatic encephalopathy (OHE)
  - Grade II - IV





## ❖ Subtypes of HE

- Minimal HE
  - No clinically detectable behavioural, cognitive or motor signs (including extrapyramidal dysfunction) of HE; diagnosed by psychomotor testing
- Diagnose when there is
  - Especially important to
    - Safety issues
    - Impact on quality of life
    - Prevent progression to covert HE (MHE plus grade I HE or overt HEV [OHE])
- Hepatic myelopathy (MH)
- HE plus cirrhosis-associated parkinsonism
  - Prominent extra pyramidal +/- pyramidal signs
  - May overlap with HM
  - Associated with brain atrophy

## Curiosities

- HE and cirrhosis-associated parkinsonism do not respond to  $\text{NH}_3$ -lowering therapy, such as lactulose

## ➤ Clinical changes

| Symptoms                                                                                                                                                                                                                                                                                                                                             | Signs                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <ul style="list-style-type: none"> <li>○ Attention</li> <li>○ Cognition, consciousness, confusion</li> <li>○ Discrementation</li> <li>○ Memory (working)</li> <li>○ Motor</li> <li>○ Personality</li> <li>○ Sleep disturbance</li> <li>○ Seizures</li> <li>○ Visuopatial</li> </ul>                                                                  | <ul style="list-style-type: none"> <li>○ Motor               <ul style="list-style-type: none"> <li>- ↑ tone</li> <li>- Babinski sign (up-going toes)</li> <li>- Asterixis</li> </ul> </li> <li>○ Extrapyramidal               <ul style="list-style-type: none"> <li>- Rigidity</li> <li>- Brady / hypokinesia</li> <li>- Tremor</li> <li>- Dyskinesia</li> <li>- Tremor</li> <li>- Dyskinesia</li> <li>- Monotony</li> <li>- ↓ voluntary movements</li> </ul> </li> <li>○ Psychometric changes (need to diagnosis preclinical / minimal hepatic encephalopathy)</li> <li>○ Rarely               <ul style="list-style-type: none"> <li>- Focal neurological deficit</li> </ul> </li> </ul> |
| <ul style="list-style-type: none"> <li>○ The possibility is always considered that the person at risk for HE might have a coagulopathy and / or have fallen, and developed an intracranial hemorrhage (ICH)</li> <li>○ A past history of ICH or the presence of focal neurological signs might also suggest ICH in the cirrhotic patient.</li> </ul> |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |



### Clinical Gem

- Give the clinical presentation which signals the beginning of overt hepatic encephalopathy.
  - Disorientation
  - Asterixis
- Give the classification represented by the flapping tremor (asterixis) of HE.
  - Asterixis is not a tremor, is “Is a negative myoclonous consisting of loss of postural tone” (Vilstrup et al. Hepatology 2014; 60: 718)

### ➤ Subtypes

#### MCQ Alert

- Give the subtypes of hepatic encephalopathy with pronounced pyramidal/extrapyramidal signs, brain atrophy, and failure to respond to NH<sub>3</sub>-lowering drugs.
  - Cirrhosis-associated parkinsonism
- Give the subtype of hepatic encephalopathy
  - In which the motor abnormalities are worse than the mental dysfunction
  - Fails to respond to NH<sub>3</sub>-lowering medications such as lactulose and antibiotics
  - Does respond to liver transplantation
- Hepatic myelopathy is characterized clinically by spastic, weak by muscle, paraplegia, plus mild persistent/recurrent mental changes.

#### Concept Change

- While most symptoms/signs of overt hepatic encephalopathy are reversible, except in the context of the two subtypes hepatic myelopathy, and cirrhosis-associated parkinsonism, even in the classical types of HE the defects in learning and working memory may persist with repeated episodes of overt hepatic encephalopathy (ORE)

### ➤ Risk stratification / severity

#### ❖ Near-normal level of consciousness (LOC) **West Haven Criteria**

- |                |                                                           |
|----------------|-----------------------------------------------------------|
| – Covert (CHE) |                                                           |
| ▪ Minimal      | – Abnormal psychometric / neuropsychological tests        |
| ▪ Grade I      | – Altered behaviour / cognition (B / C)                   |
| – Overt (OHE)  |                                                           |
| ▪ Grade II     | – B/C changes, plus disorientation in both time and place |
| ▪ Grade IV     | – Comatose, unresponsive (use Glasgow coma scale [GCS])   |



## ❖ Significant alteration in LOC: Glasgow coma scale (GCS)

- Time course
  - Episodic bouts recur within > 6 mon
  - Recurrent bouts recur within < 6 mon
  - Persistent
- Precipitating factors
  - Idiopathic                      ■ Spontaneous
  - Infection                        ■
  - Infiltration                      ■ HCC
  - Iatrogenic                       ■ Drugs, alcohol
  - Injury                            ■ Surgery
  - TIPS
  - Bleeding
  - Ischemia                        ■ BCS
  - PVT
  - Metabolic                       ■ Electrolyte disturbance
  - Constipation

For each Column, Circle Appropriate Term

| Type | Grade    |         | Time Course | Precipitating Factor               |
|------|----------|---------|-------------|------------------------------------|
| A    | MHE<br>1 | Convert | Episodic    | Spontaneous (idiopathic)           |
|      |          |         | Recurrent   |                                    |
| B    | 2        | Overt   | Persistent  |                                    |
|      | 3        |         |             | Injury precipitated (specify what) |
| C    | 4        |         |             |                                    |

## ➤ Testing strategies for OHE and CHE testing

- Establish presence of acute liver failure, portosystemic shunting or bypass or cirrhosis
- Exclude non-hepatic causes of brain dysfunction / ↓ level of consciousness (LOC) e.g.
  - Alcohol                      – ↓ Na<sub>s</sub><sup>+</sup>
  - Drugs                        – Psychiatric disease
- Identify possible precipitants of HE
- Diagnose and grade HE
  - PSE (aka PHES), CFF, CRT, ICT, Stroop test, scan test, EEG

Note: blood (NH<sub>3</sub>) does not add to diagnosis staging or prognostic value.

Note for Canadian Readers: Testing knowledge of the details of the following tests for overt (OHE) and covert hepatic encephalopathy should be outside the reasonable realm of testing of Royal College of Physician and Surgeons examination in General Internal Medicine or in Gastroenterology.

- Portosystemic encephalopathy (PSE) syndrome test
- Criteria flicker frequency (CFF) test
- Continuous reaction time (CRT) test



- Inhibitory control test (ICT)
- Stroop test
- Scan test
- Electroencephalopathy (EEG) cortical cerebral activity changes

#### Remember

- Psychometric tests detect early overt HE, but do not establish the cause of the defects

#### ➤ Laboratory

- While “high blood-ammonia [ $\text{NH}_3$ ] levels do not add any diagnostic, staging, or prognostic value in HE patients with CLD ..., [in the presence of a normal  $\text{NH}_3$  concentration], ... the diagnosis of HE is in question” (Vilstrup et al. Hepatology 2014; 60: 722).
- Even in the presence of possible clinical (MELD score) or laboratory features (platelets, INR, creatinine concentration), there was no predictive benefit
- The authors suggest that even in the presence of abnormal hemostatic indices, patients with even a high score for Model for End-Stage Liver Disease on no focal neurological signs or trauma, “...have a low likelihood of ICH” (intracranial hemorrhage).

#### ➤ Diagnostic imaging

- Non-contrast CT scanning is the initial imaging study of choice for ICH.
- However, the number of CT scans needed to achieve one positive result (NNS) was high and depended upon the indication
  - Focal neurological signs 9
  - Fall / trauma 20
  - Altered mental status 293

#### ➤ Treatment

- Suspected HE in a patient with CLD



- Exclude mimicking conditions



- Subdural hematoma
- Brain tumour
- Stroke
- Epilepsy
- Dementia
- Delirium
- Psychiatric disorders
- Drug-toxicity
- Encephalitis

- Metabolic conditions
- Renal dysfunction
- DM plus HCV
- Obstructive sleep apnea (OSA)

- Wernicke encephalopathy
- Hypoglycemia
- Ketoacidosis
- Lactate acidosis
- Hyperosmotic coma
- Hyponatremia

- Classify re: type, grade, time, course, precipitating factors



- ↓
- Where appropriate undertake testing strategy
- ↓
- Correct precipitating factors (effective in ~ 90%)
  - Precipitating factors “I-BCDE”
    - Infection, bleeding, constipation, drugs (diuretics, opioids, benzodiazepines), electrolyte disorders
    - Note
      - Sepsis and hyponatremia can produce encephalopathy by themselves, as well as precipitating encephalopathy in the person with liver disease (HE)
- ↓
- Empiric therapy indications
 

|                                                                                                                                                                                                                                                                                                |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <ul style="list-style-type: none"> <li>– MHE, CHE: Rx case-by-case; OHE</li> <li>– Prophylaxis               <ul style="list-style-type: none"> <li>▪ 2<sup>o</sup> prophylaxis after OHE</li> <li>▪ 1<sup>o</sup> primary cirrhosis plus known high risk to develop HE</li> </ul> </li> </ul> | <ul style="list-style-type: none"> <li>– Lactulose (acute and maintenance)               <ul style="list-style-type: none"> <li>▪ 25 - 30 mL po q 1-2 until 2-3 loose BM/d</li> <li>▪ Neomycin</li> <li>▪ Metronidazole</li> <li>▪ Energy intake                   <ul style="list-style-type: none"> <li>– 35 - 40 kcal/kg, plus</li> <li>– Protein (milk/vegetable) 1.2 - 1.5 g/kg/day</li> </ul> </li> </ul> </li> <li>▪ Vitamins (thiamine if risk of Wernicke’s)</li> </ul> |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
- ↓
- Antibiotics
    - Metronidazole
    - Neomycin
    - Rifaximin
    - Rifaxin plus lactulose for maintenance
      - Oral BCAA enriched formulations or IV LOLA
      - Intractable OHE plus liver failure: carefully excluded

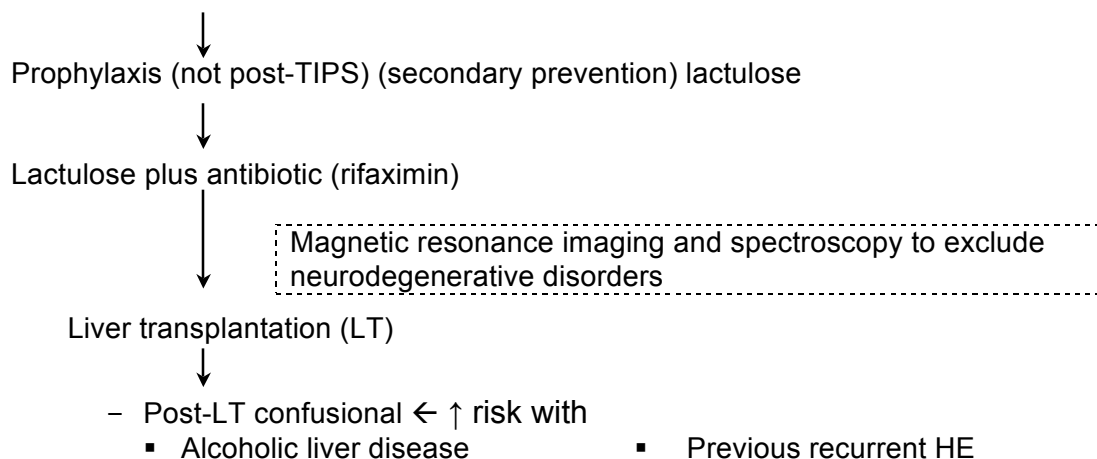
Abbreviations: BCAA, branched-chain amino acids; BMs, bowel movements; CLD, chronic liver disease; DM, diabetes mellitus; HCV, hepatitis C virus; OSA, obstructive sleep apnea

- Correction of protein-calorie malnutrition
  - With frequent small meals
  - Oral BCAA-enriched formula supplementation
- Energy 35-40 kcal/kg 1 BW/d
- Protein 1.2 – 1.5 g/kg/d, including milk / vegetable-based protein
  - Correction of specific deficiencies e.g., thiamine, folic acid, iron, calcium

↓ persistent HE

IV – L-ornithine L-aspartate (LOLA)





Abbreviations: ACLF, acute-on-chronic liver failure; BCAA, branched-chain amino acid formulations; CFF, critical flicker frequency test; CHE, convert HE; CRT, continuous reaction time; EEG electroencephalopathy; HE, hepatic encephalopathy; IBW, ideal body weight; ICT, inhibitory control test; ISHEN, International Society for Hepatic Encephalopathy and Nitrogen Metabolism; LOC, level of consciousness; LOLA, L-ornithine L-aspartate; LT, liver transplantation; MHE, minimal hepatic encephalopathy;  $\text{Na}_s^+$ , serum sodium concentration; OHE, overt HE (grade II-IV HE); PHES, psychometric hepatic encephalopathy score; PSE, portosystemic encephalopathy syndrome test

#### Clinical Tip

- Give reasons for an unexpectedly poor improvement in symptoms of hepatic encephalopathy in a patient with cirrhosis plus HE and liver transplantation (LT).
  - Associated neurodegenerative disorder
  - Peri-/post-operative stroke, seizure
  - Uncorrected deficiencies e.g., thiamin
  - Large untreated portosystemic shunts
  - Encephalitis/immunosuppression
  - Post-LT confusion syndrome
- There is ↑ risk of bacterial infection in patients who are cirrhotic, and this risk continues in the post liver transplantation era
- Patients given pre-/ probiotics, before or on the day of LT develop fewer infections, used antibiotics for a shorter time (3.9 d), spent less time in the ICU (1.4 d) and in hospital (1.4 d), and had fewer infections

| Feature           | Pre- / Proantibiotics | Controls |
|-------------------|-----------------------|----------|
| - Infection rate  | 7%                    | 35%      |
| ▪ Urinary tract   | 2%                    | 16%      |
| ▪ Intra-abdominal | 2%                    | 11%      |

- It is speculated that by altering the intestinal microbiome with pre- / proantibiotics, there is enhancement of the components of the intestinal barrier, with less translocation of harmful bacteria.



## AUTOIMMUNE HEPATITIS (AIH): EASL GUIDELINES

Abbreviations: AASLD, American Association for the Study of Liver Diseases; BSG, British Society of Gastroenterology; EASL, European Association for the Study of the Liver Diseases

AASLD Guidelines: Manns MD, et al. Hepatology 2010; 51: 1-31; BSG Guidelines: Gleeson D and Heneghan M. Gut 2011; 60(12):1611-29; EASL Guidelines: J Hepatology 2015; 63: 971-1004; Vierling JM. Clin Gastroenterol Hepatol 2015; 13: 2088-2108.

- Demography
  - Prevalence
    - Highly variable ~ 20/10<sup>5</sup>
- Clinical presentation
  - There may be long asymptomatic intervals of AIH both before (~30%) and after diagnosis
  - Acute
    - True acute                                      - Zone 3 necrosis (centrilobular [central] perivenulitis)
    - Acute on chronic
  - During / after pregnancy
    - May be serology (antibody) negative
  - Post LT for AIH ("post-transplantation plasma cell hepatitis")
    - Poorer than usual response to corticosteroids
  - De novo post LT for other type of liver disease
  - Associated with viral hepatitis
- Types
  - AIH-1 (90%)
    - Serology
      - ANA (43%)
      - SMA (anti-F actin, 41%)
      - Anti-SLA / LP (high diagnostic value)
    - HLA
      - DR3 and DR13
    - Responds well to treatment
  - AIH-2 (10%)
    - Serology
      - Anti-LC1
      - Anti-LKM1
      - Anti-LKM3
    - HLA
      - DR3 and DR7
    - Young persons (more common in German)
    - Frequent relapses / treatment failures
    - Long-term maintenance required
  - AIH-3 (~1%)
    - Serology
      - Anti-SLA / LP
    - Response well to treatment



- APS-1
  - Associated with autoimmune polyendocrinopathy candidiasis ectodermal dystrophy
- Overlap / variant forms
  - AIH plus PBC / PSC / DILI
  - In children
    - Autoimmune sclerosing cholangitis (AISC)
- IgG4-related AIH

Clinical suspicion of AIH → negative AMA, SMA, LKM1 / LC1, SLA / LP (indirect immunofluorescence [IFL]) → pANCA

- ELISA / immunoblotting
  - F-actin, LKM / LC1, SLA / LP, Ro52, gp210, gp100

Abbreviations: ANA, anti-nuclear antibodies; APS-1, autoimmune polyglandular syndrome type 1; HLA, human leukocyte antigen; LC1, liver cytosol type 1 antigen; LKM1, liver / kidney microsomal antibody type 1; LKM3, liver / kidney microsomal antibody type 3; SLA / LP, soluble liver antigen / liver pancreas; SMA, smooth muscle antibodies

#### Overlap (“Variant”) Forms of AIH

##### ❖ AIH-PBC (primary biliary cirrhosis) variant

- AIH
  - Biochemistry
    - ALT  $\geq$  5x ULN
    - IgG  $\geq$  2x ULN
  - Serology
    - SMA-positive
  - Histopathology
    - Periportal / periseptal lymphocyte piecemeal necrosis
- PBC
  - Biochemistry
    - AP  $\geq$  2x ULN, or
    - GGT  $\geq$  5x ULN
  - Serology
    - AMA positive
  - Histopathology
    - Florid bile duct lesions
- Performance characteristics (“Paris Criteria”)
  - Sensitivity 92%
  - Specificity 97%

##### ❖ AIH-PSC (primary sclerosing cholangitis) variant

- Less well-defined criteria
- 10% of AIH patients +/- ulcerative colitis may have bile duct injury on histology
- Bile duct imaging on diagnostic image (especially small duct intrahepatic changes) has a wide differential diagnosis, particularly if intrahepatic, and associated with
  - Extensive fibrosis
  - Nodular regeneration
  - Cirrhosis
- MRCP changes of large duct changes are not specific (may be false-positive)





- ❖ AIH-DILI (drug-induced liver liver)
  - AIH-DILI is a cause of ~ 10% of cases of AIH
  - Differentiate
    - Both AIH and AIH+DILI response to prednisone 0.5 - 1 mg/kg
    - When prednisone tapered, AIH+DILI does not recur, whereas AIH does recur within a couple of months
  - Commonly associated drugs
    - Antibiotics
      - Minocycline
      - Nitrofurantoin
    - Anti-immunity
      - A-TNF inhibitors
      - Interferon
- Diagnostic criteria (in adults)
- ❖ International Autoimmune Hepatitis Group (IAIHG) Diagnostic Score for AIH

|                                            | Definite AIH | Probable AIH |
|--------------------------------------------|--------------|--------------|
| ○ Biochemistry                             |              |              |
| - ALT / AST abnormality                    |              |              |
| - Gamma-globulins / IgG                    | > 1.5x ULN   | Any ↑        |
| ○ Liver histopathology (moderate / severe) |              |              |
| ○ Serology                                 |              |              |
| - ANA, SMA, anti-LKMI                      | > 1:80       | > 1:40       |
| ○ Rule out other liver conditions          |              |              |
| - Alcohol                                  | > 25 g/d     | > 50 g/d     |
| - Hepatitis A, B, C (acute infection)      |              |              |
| - Recent hepatotoxic drugs                 |              |              |
| - Iron, ferritin                           |              |              |
| - Ceruloplasmin                            |              |              |
| - α-AT phenotype                           |              |              |

Adapted from: EASL Clinical Practice Guidelines. J Hepatology 2015; 63: page 978, Table 5

“What is not started today is never finished tomorrow.”

Johann Wolfgang von Goethe



## ❖ Simplified IAIHG Diagnostic Score

|                                                                        | Definite AIH                                                                                                                                         | Probable AIH |
|------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------|--------------|
| ○ Biochemistry                                                         |                                                                                                                                                      |              |
| – Gammaglobulin / IgG                                                  | > ULN<br>> 1.1x ULN                                                                                                                                  | +1<br>+2     |
| ○ Serology (maximum of 2 points in total score can come from serology) |                                                                                                                                                      |              |
| – ANA+ or SMA+                                                         | ≥ 1:40<br>≥ 1:80                                                                                                                                     | +1<br>+2     |
| Or                                                                     |                                                                                                                                                      |              |
| – LKM+                                                                 | ≥ 1:40                                                                                                                                               | +2           |
| Or                                                                     |                                                                                                                                                      |              |
| – SLA / LP absence of viral hepatitis                                  | Any titre<br>No<br>Yes                                                                                                                               |              |
| ○ Diagnostic certainty (AIH)                                           | – Definite<br>– Probable                                                                                                                             | ≥ 7<br>≥ 6   |
| ○ Histopathology                                                       |                                                                                                                                                      |              |
| – Chronic hepatitis                                                    |                                                                                                                                                      |              |
| ▪ Atypical                                                             |                                                                                                                                                      | 0            |
| ▪ Compatible                                                           | – Interface hepatitis<br>– Lymphocytic infiltration                                                                                                  | +1           |
| ▪ Typical                                                              | – Interface hepatitis<br>– Lymphocytotoxic infiltration in portal tracts →<br>– Lobules / penetration of one cell into a larger cell (emperipolesis) | +2           |

## ➤ Histopathology

- No pathognomonic feature(s)
  - Cholangitis
  - Granuloma
  - Steatosis / steatohepatitis



- Hepatitis
  - Lymphoplasmocytic infiltration at the interface (not necessarily in the inflammatory infiltrate)
    - Porto-parenchymal
    - Panacinar (parenchymal collapse)
    - Pericentral (zone 3)
  - Portal lymphoid follicles
  - Perivenulitis
- Hepatocytes
  - Rosette formation
  - Emperiolesis (small cell penetrates into longer cell)
  - Necrosis
  - Bridging
  - Massive
- Less common features
  - Cholangitis
  - Granuloma
  - Steatosis / steatohepatitis
- Macronodular cirrhosis

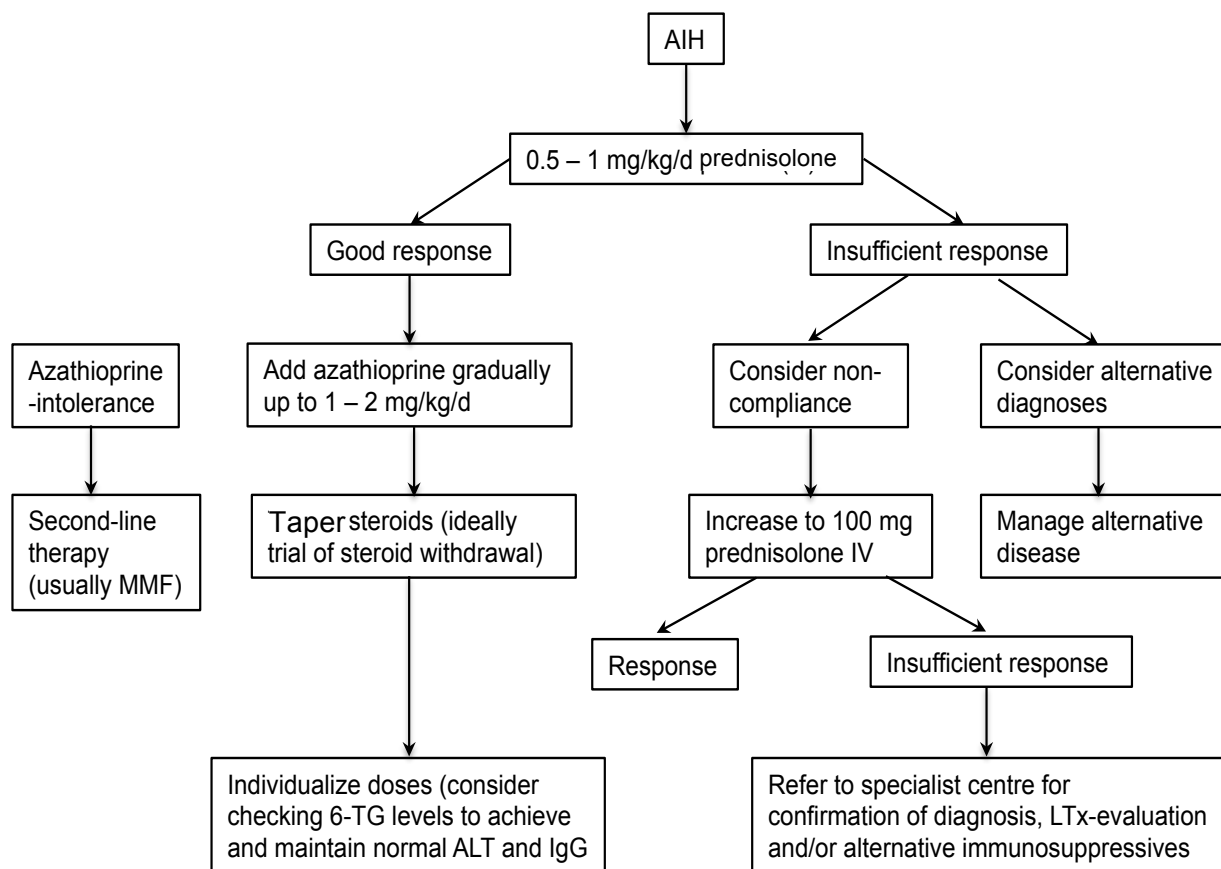
➤ Treatment

- Among the various goals of treatment of AIH is the resolution of the activity of the hepatitis, which can be obtained by performing a liver biopsy (hepatitis activity index, HAI, 5 – 6).
- The laboratory tests, which are reliable surrogate markers for resolved hepatitis are the normalization of both ALT / AST plus IgG levels.
- Indications
 

|                                                                                                                                                                                                               |                                                                                                                                                                                                                                                                                                                                                   |                                                                                                                                     |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------|
| <ul style="list-style-type: none"> <li>- Mildly active hepatitis</li> <li>- Moderately active hepatitis</li> <li>- Compensated</li> <li>- Decompensated cirrhosis</li> <li>- Spontaneous remission</li> </ul> | <ul style="list-style-type: none"> <li>▪ <math>\uparrow</math> ALT &lt; 3x ULN</li> <li>▪ AAI &lt; 4 / 18</li> <li>▪ No advanced fibrosis</li> <li>▪ HAI <math>\geq</math> 4 / 18</li> <li>▪ Fibrosis / cirrhosis (high inflammatory score)</li> <li>▪ Low activity score</li> <li>▪ Follow q 3-6 mon and treat necessary reactivation</li> </ul> | <div style="font-size: 3em;">}</div> <div style="display: inline-block; vertical-align: middle;">Induction treatment optional</div> |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------|



# ❖ Therapeutic Strategy in Autoimmune Hepatitis

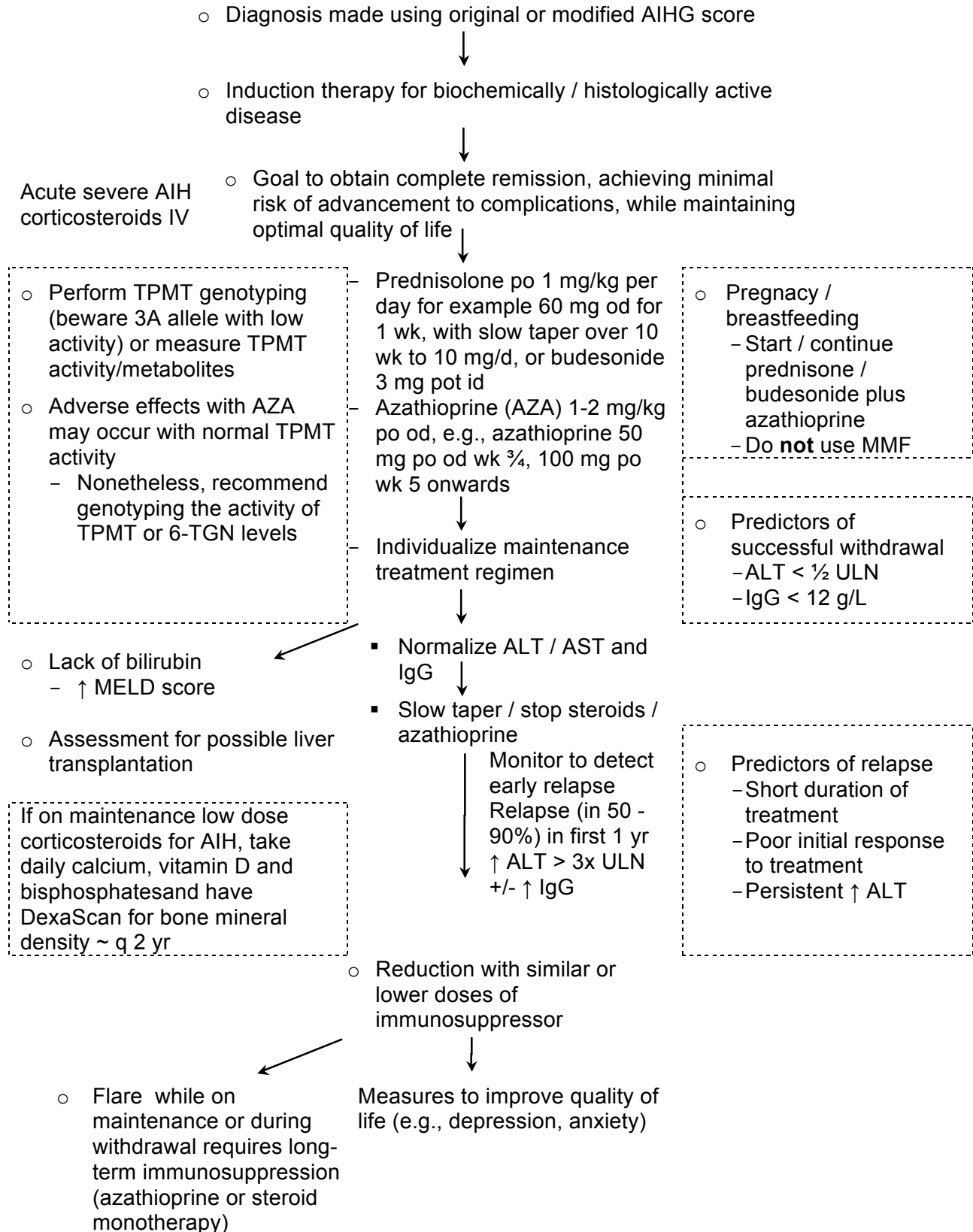


Printed with permission: EASL, J. Hepatology 2015; 63: 971-1004.

“Be aware of the big picture in the patients’ life, not just blinkers on the obvious medical problem.”

Dr. Joel Huurwitz





Abbreviations: IAIHG, International Autoimmune Hepatitis Diagnostic Score



## Special Considerations

### ❖ The elderly

- Give the difference in AIH in the elderly.
  - Because of these age-associated issues of AIH, it is best to treat the elderly patient with mild interface activity and low necroinflammatory scores on liver biopsy
    - ↓ symptoms
    - ↓ response to therapy
    - ↑ HLA DR4 alleles
    - ↑ risk of cirrhosis
    - ↑ risk of concurrent autoimmune disease

### ❖ Non-response

#### ➤ Definition

- ↓ ALT < 25% after 2 wk of initial treatment with corticosteroids

#### ➤ Causes / associations

- Non-adherence to medication plan
- Attenuate diagnosis
- Old age
  - ↓
  - of an budesonide, switch to prednisone
  - ↑ disease of prednisone / azathioprine / 6-MP
    - Target 6-TG leads to  $> 220 \text{ pmol} \times 8 \times 10^8$
  - ↓ Continued poor response
  - Cyclosporin, or tacrolimus (MMF)
  - ↓

#### Consider possible overlap syndrome

- De novo AIH post-liver transplantation
  - Standard management with prednisone / azathioprine
- HBV / HCV
  - Vaccinate against HAV / HBV before treating AIH
  - If AIH plus HBV / HCV virus replication
    - Treat HBV / HCV first and without interferon (e.g., entecavir or tenofovir for HBV, then treat AIH)
  - If AIH plus HBsAg-positive
    - Test for HBV DNA, give nucleoside / nucleotide analogs during immunosuppression regardless of HBV DNA levels for 12 mon after completion of immunosuppression
- AIH plus HIV
  - Highly active antiviral therapy (HAART)
  - Perform liver biopsy to ensure AIH is correct diagnosis
  - Specialist referral (ID expert plus hepatologist) to benign / monitor immunosuppression



## AUTOIMMUNE HEPATITIS (AIH): AASLD GUIDELINES

Abbreviations: AASLD, American Association for the Study of Liver Diseases

Manns MP, et al. Hepatology 2010; 51: 1-31.

- Diagnostic criteria for AIH
  - Based on clinical, laboratory and histological changes
  - Because AIH may be a hepatic diagnosis of exclusion, it is useful to use a scoring system, such as SIAHG
    - Aggregate score

| Diagnosis  | Pre-Rx  | Post-Rx |
|------------|---------|---------|
| – Probably | 10 – 15 | 12 – 17 |
| – Definite | > 15    | > 17    |

- When
  - Negative first-line conventional serological tests are negative
  - Second-line tests (F-actin, LC1, LKM3, SLA / LP) are performed, and
  - If there are associated multiple endocrine disorders, exclude autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED) syndrome



- Exclude overlap conditions
  - Primary biliary cirrhosis (PBC)
    - AMA; PDH-E2; characteristic liver biopsy
  - Primary sclerosing cholangitis (PSC)
    - Atypical pANCA; MRCP / ERCP demonstration of multiple intra- / extrahepatic strictures of biliary tract characteristic liver biopsy
  - Pretreatment vaccinations with live viruses
  - Standard screening for TB, HBV



- Immunosuppression

- ❖ Indications
  - AST / ALT
    - 10x ULN, or
    - 5x ULN plus d-globulins > 2x UNL, +/-
  - Histological features: necrosis
    - Bridging
    - Multilobular
  - Incapacitating symptom
- ❖ Choices
  - Prednisolone, or prednisone plus azathioprine
- Stratify risk of adverse outcomes at presentation
  - Relapse (50 - 90%)
    - Long duration of symptoms
    - ↑ IgG, LICM+, SLA / LP+; or no immune markers
  - Progression to fibrosis / cirrhosis (10 - 50%)
    - ↑ INR
    - ↓ albumin
    - Confluent necrosis



- LT / liver-related death (2 - 20%)
  - Female
  - African males
  - Type 2, SLA+
  - Cirrhosis
  - Confluent necrosis

#### ❖ Induction Therapy

- Reasons for choice
  - Monotherapy with prednisone
    - Relative contraindication for azathioprine
      - TPMT deficiency
      - Cytopenia ( $\text{WBC} < 2.5 \times 10^9 / \text{L}$ , or platelets  $< 50 \times 10^9 / \text{L}$ )
      - Pregnancy
      - Malignancy
  - Prednisone plus azathioprine (combination)
    - Prednisone
      - For induction of remission

| Wk | mg/d      |
|----|-----------|
| 1  | 30        |
| 2  | 20        |
| 3  | 15        |
| 4  | $\leq 15$ |
    - Azathioprine
      - For induction and maintenance of remission
      - Azathioprine 50 mg/d (AASUE) 1-2 mg/kg per day (BSE)

#### ❖ Maintenance of Remission

- Note:
  - In patients being placed on azathioprine (AZA); test for TPMT deficiency, as well as perform regular testing of WBC
  - Where available, test for metabolites of AZA / 6-mercaptopurine
  - Combination therapy with prednisone plus azathioprine
    - Relative contraindications to long course ( $> 6$  mon) of prednisone
      - Osteoporosis            - Obesity
      - Diabetes                - Emotional liability / psychosis



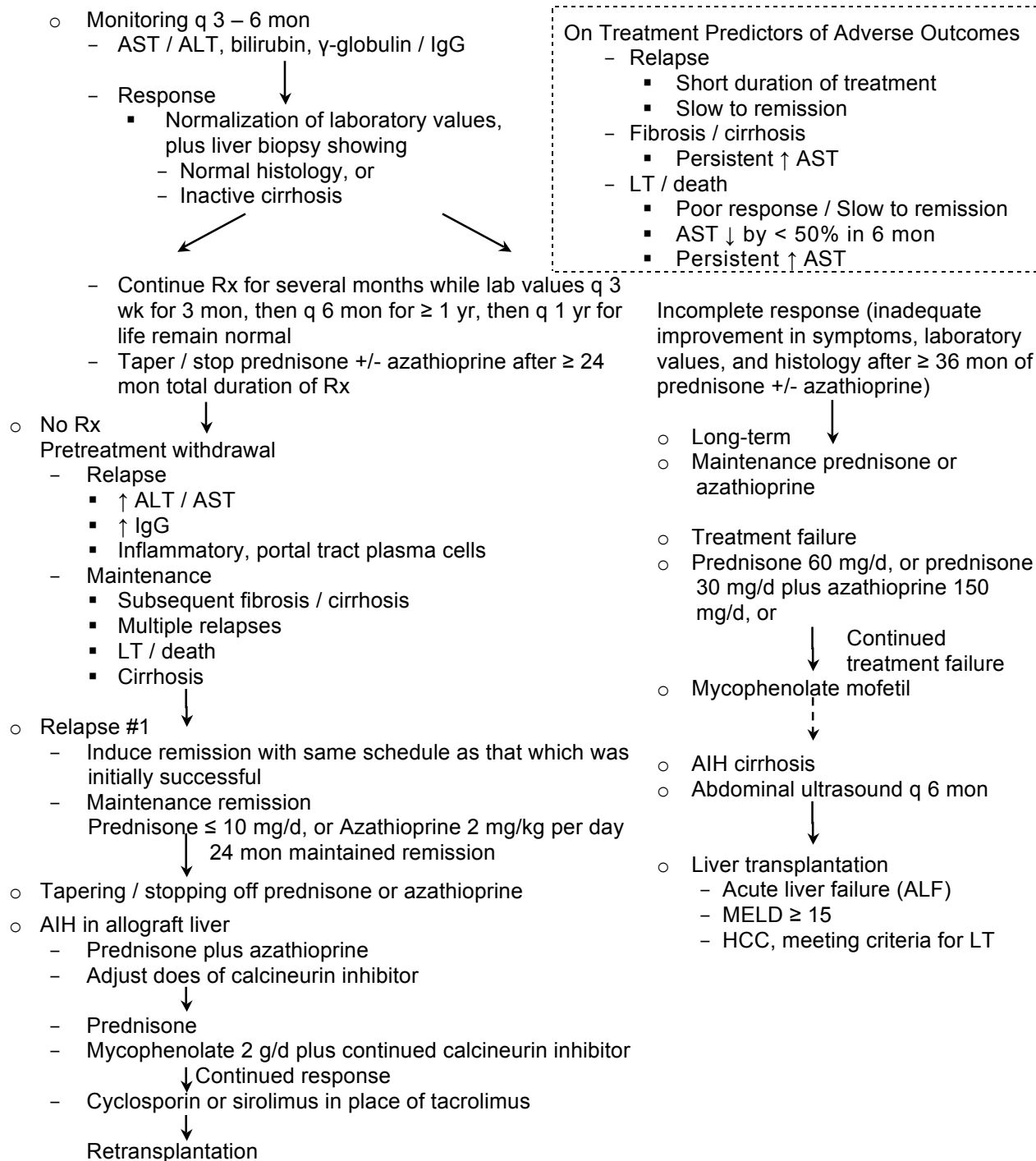
- Dose regimens
  - Prednisone (monotherapy) for induction of remission
  - For maintenance of

| Wk                           | mg/d      |
|------------------------------|-----------|
| 1                            | 60        |
| 2                            | 40        |
| 3                            | 30        |
| 4                            | 30        |
| For maintenance of remission | $\leq 15$ |

- Targets / end points / Rx stopping rules







Abbreviations: ALF, acute liver failure; AMA, antimitochondrial antibody; ANA, antibody to antinuclear antibody; anti-LC, antibody to liver cytosol type 1; anti-LKM1, antibody to liver / kidney microsomes type 1; anti-SLA, antibody to soluble liver antigen; F-actin, antibodies to actin; HCC, hepatocellular cancer; HLA, human leukocyte antigen; IAHE, International Autoimmune Hepatitis Group; IgG, immunoglobulin G; LKM-3, liver / kidney microsomes type 3; LM, liver microsome; pANCA, perinuclear anti-neutrophil cytoplasmic antibody; PBC, primary biliary cirrhosis; PDHE2, E2 subunits on the pyruvate dehydrogenase complex; PSC, primary sclerosing cholangitis; Rx, pharmaceutical treatment; SAL / LP, soluble liver antigen / liver pancreas; SMA, smooth muscle antibody; TPMT, thiopurine methyltransferase deficiency; WBC, white blood cell count



## ASCITES

### ➤ Demography

- Commonest complication of hepatic cirrhosis (together with hepatic encephalopathy and bleeding esophageal varices)
- 50% of patients with cirrhosis will develop ascites within 10 yrs

### ➤ Clinical

- Amount of ascites present before flank dullness detected ~ 1500 mL
  - No flank dullness: < 10% likelihood of ascites being present (i.e., high sensitivity)
- Shifting dullness
  - Performance characteristics (for ascites)
    - Sensitivity ~80%
    - Specificity ~ 55%

## Guidelines of the American Medical Association (JAMA)

### SN signs

- Ankle swelling (LR 2.8)
- ↑ abdominal girth (LR 4.6)
- Bulging flanks
- Shifting dullness
- Flank dullness

### SP signs

- Fluid wave (LR 0.4)
- Shifting dullness
- Peripheral edema (LR 0.1)

Abbreviations: LR, likelihood ratio; SN, sensitivity; SP, specificity

### Laboratory Tip

- Brain natriuretic peptide (BNP) is ↑↑ in HF with ascites, but not so much in cirrhosis with ascites (median values, pg/mL of 6100 vs 166 respectively), except in cases of cardiac cirrhosis.

### Diagnostic Imaging Gem

- Give the reasons why an abdominal ultrasound is often indicated in the patient with cirrhosis.
  - Liver
    - Size
    - Radiological signs of cirrhosis
    - Detection of fatty infiltration to suggest NAFLD
  - Spleen
    - Splenomegaly
  - Complications of cirrhosis
    - Ascites
    - Hepatocellular cancer (HCC)
    - Hepatic vein thrombosis / Budd-Chiari syndrome (BCS)
    - Portal vein thrombosis (PVT)
    - Signs of portal hypertension (PHT)



### Clinical Pearl and Gem

- Give the position of the anterior abdominal wall where it is best to perform a paracentesis.
  - Left lower quadrant
    - 3 cm above
    - 3 cm medial to

} Anterior superior iliac spine

### ➤ Risk factors

- Assess risk for hepatorenal syndrome (HRS)
  - ↑ urinary neutrophil gelatinase-associated lipocalin (UNGAL)

| Group      | ng/mL |
|------------|-------|
| ▪ Normal   | 20    |
| ▪ Prerenal | 20    |
| ▪ CRF      | 50    |
| ▪ HRS      | 105   |
| ▪ AKI      | 325   |

Abbreviations: AKI, acute kidney injury; CRF, chronic renal failure; HRS, hepatorenal syndrome

### ➤ Differential diagnosis (of causes of ascites)

- Disease of
  - Liver
    - Acute / chronic liver disease
  - Heart
    - Heart failure
  - Kidney
    - Nephrotic syndrome
  - Peritoneum
    - Tuberculosis, carcinomatosis
  - Thyroid
    - Myxedema
  - Others
    - Hypoalbuminemic state
  - Note: Proportion of patients with cirrhosis
    - ≥ 2 causes of ascites 5%
    - A non-cirrhotic cause of ascites 15%

### Trick Question

- Give the value of the INR of a patient with cirrhosis which is a contraindication for performance of paracentesis.
  - Because of the balance of deficiencies of both procoagulants as well as anticoagulants in patients with cirrhosis, the INR is a measure of hepatic function, rather than a reflection of the patient's coagulation status.

"There is no data-supported cut-off of coagulation parameters beyond which paracentesis should be avoided" (Runyon BA. Hepatology 2013; 54: page 3).

### Abdominal Paracentesis

- Even in the presence of ↑ INR, only ~1% of persons having abdominal paracentesis develop complications
  - Minor
    - Hematoma
  - Serious (< 1/10<sup>3</sup>)
    - Hemoperitoneum and puncture of intestine



➤ Laboratory

- In the patient with ascites, the serum-ascites albumin gradient (SAAG)  $\geq 1.1$  g/dL is 97% accurate for diagnosing portal hypertension.
  - Diuretics or IV fluid infusion have no effect on the accuracy of SAAG.
- In the absence of portal hypertension (SAAG  $< 1.1$  g/dL), only persons with ascites due to nephrotic syndrome will respond to salt restriction and diuretics.
- Peritoneal carcinomatosis causing ascites is most common with primary malignancies from the breast or GI tract (stomach, pancreas, colon).
- Give the sensitivity of cytology on 3 separate paracenteses to diagnosis peritoneal carcinomatosis.
  - Smear  $< 1\%$
  - Culture  $\sim 50\%$

Superior tests for TB would include

- PCR testing
- Laparoscopic biopsy of peritoneum

More laboratory Gems

- The concentration of neutrophils in an ascitic fluid aspiration which is used to diagnose SBP is  $\geq 250$  cells/mm<sup>3</sup> ( $0.25 \times 10^9$  /L). Give what is the likelihood of having culture positive SBP in patient with ascetic neutrophil count of more than 250 cell/mm<sup>3</sup>.
  - Inoculation of fluid at the bedside into the blood culture bottles – 80%
  - Any other method of inoculation – 50%
- Give the number of days / dose of antibiotics which will result in negative cultures of ascitic fluid neutrophils  $\geq 250$  cells/mm<sup>3</sup>.
  - Only one dose of antibiotics may cause the culture of infected peritoneal fluid to be negative.

➤ Prognosis

- Best predictor of mortality in patients with cirrhosis
  - Mean arterial pressure (MAP)

| Value of MAP (mm Hg) | 1 yr Mortality Rate |
|----------------------|---------------------|
| $> 82$               | 30%                 |
| $\leq 82$            | 60%                 |

“Cirrhosis cures [systemic] hypertension”, but lowering blood pressure may reduce survival.

- Mortality in cirrhosis with ascites
 

|      |     |      |     |
|------|-----|------|-----|
| 1 yr | 15% | 5 yr | 44% |
|------|-----|------|-----|

Tips Against

- In patients with cirrhosis with ascites
  - Do not insert
    - Chest tube for hepatic hydrothorax
    - PEG (percutaneous endoscopic gastrostomy) tube (for enteral feeding)



## Management of Adult Patients with Ascites: AASLD and EASL Practice Guideline

Abbreviations: AASLD, American Association for the Study of Liver Diseases; EASL, European Association for the Liver

Runyon BA, Hepatology 2013; 54: 1-27 and 1651-1653; and EASL Clinical Practice Guidelines. J Hepatology 2010; 53: 397-417.

All cirrhotics with new ascites or on hospitalization with pre-existing ascites

- ↓
- Suspect Ascites
    - Clinical symptoms / signs
    - Abdominal ultrasound confirmation
    - Diagnostic paracentesis
      - Neutrophils, albumin / total protein concentrations
      - Glucose, LDH, amylase, Gram stain and culture
    - Spot urinalysis monitoring target (when 24 hr  $U_{Na}$  not available)
      - $Na_u^+ / K_u^+ > 1$  (urine sodium / urine potassium) → predicts 24 hr  $U_{Na} > 78$  mmol/d
  - Diet
    - $Na^+$  restriction (2 g per day [88 mmol/d])
    - No alcohol intake
    - Baclofen 5 mg po tid x 3 d, then 10 mg tid maintenance (↓ craving for alcohol)
  - Drugs to avoid
    - Non-steroidal anti-inflammatory drugs (NSAIDs) to avoid kidney injury
      - Continue aspirin if necessary for cardiac prophylaxis
    - ACEI / ARBs (angiotensin converting enzyme inhibitors / angiotensin receptor blockers)
    - Beta-blockers
    - Hydrochlorothiazides
    - Aminoglycosides (unless only antibiotics available for use against a life-threatening infection)
    - Fluid restriction to 1 L/d only if  $Na_s^+ < 120$  mmol/L (only prevents further ↓  $Na_s^+$ )
  - Diuretics
    - Aim
      - Greatest patient comfort on lowest dose of diuretics
    - Spironolactone 100 mg
    - Furosemide 40 mg

} po q AM for 3-5 /d, then slowly increase q 3-5 /d to maximum of 400 mg aldactone / 160 mg furosemide po/d
  - Give the reason why the diuretic hydrochlorothiazide should not be used in cirrhosis with ascites.
    - The recommended diuretic regimen for ascites associated with portal hypertension (cirrhosis with ascites).
    - Aldactone plus furosemide in a ration of 100 mg to 40 mg/d
    - Adding hypochlorothiazide to this regimen can rapidly cause dangerous hyponatremia

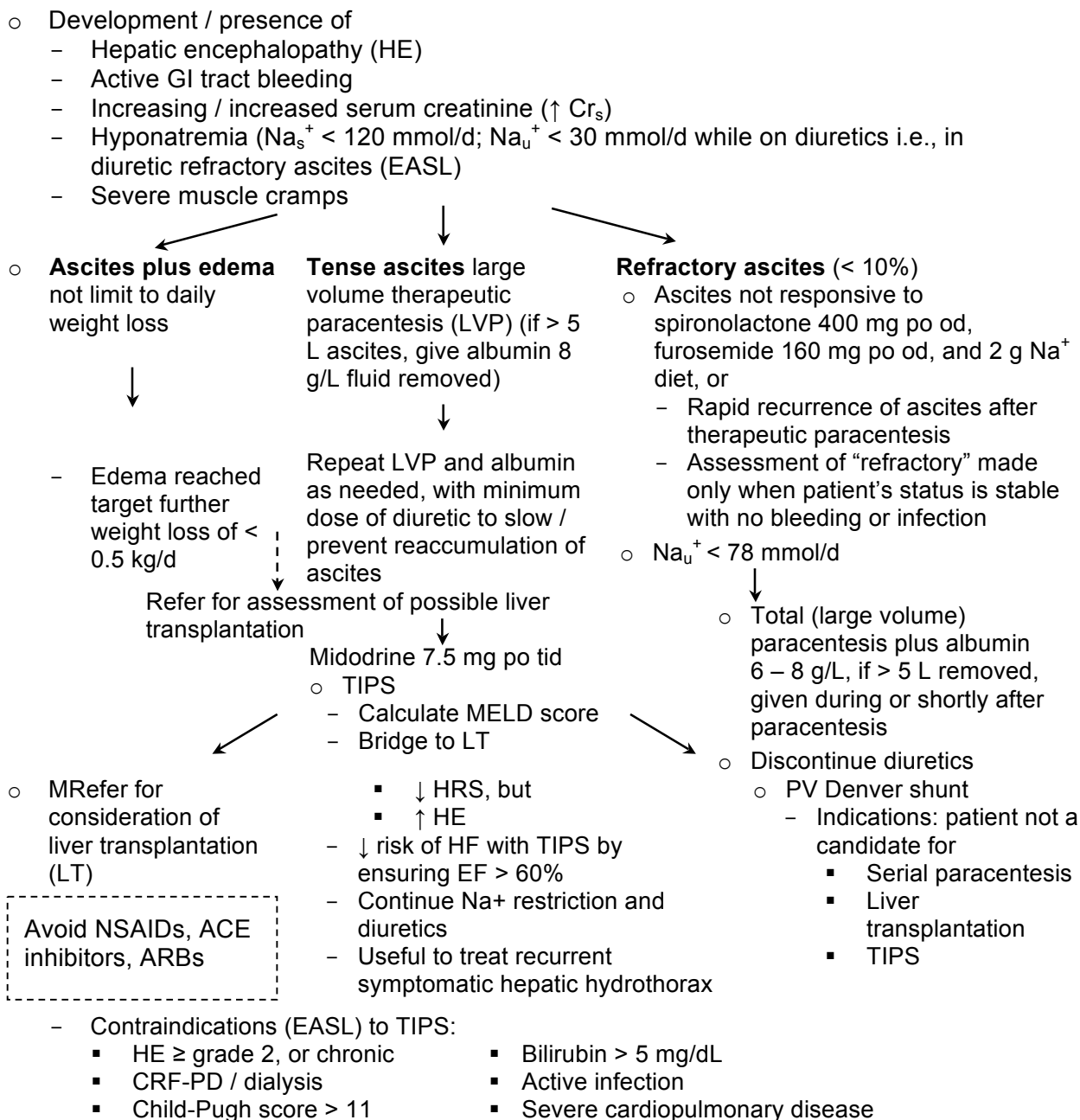
### Caution to the "Drinker" (of alcohol)

- Give the 3-yr mortality of alcoholic cirrhosis with Child-Pugh C who stop drinking vs. those who continue to drink.
  - Continue drinking > 99%
  - Cessation of drinking 25%



- In the patient who is on spironolactone plus furosemide, as well as a 2 g salt diet per day, and is not losing weight, give how to determine patient compliance to the low sodium diet.
  - A 24-hr  $\text{Na}_u^+$  of  $> 78$  mmol/d while on a 2 g Na intake indicates actual intake of  $> 88$  mmol (2 g) per day.

- Give hen to stop both spironolactone and furosemide for several days.



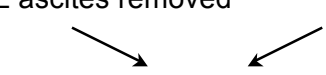
Abbreviations: ARBs, angiotensin receptor blockers; CRF, chronic renal failure, parenchymal disease;  $\text{Cr}_s$ , serum creatinine; EF, (cardiac) ejection fraction; HE, hepatic encephalopathy; HRS, hepatorenal syndrome; LT, liver transplantation; LVP, large volume paracentesis; MELD, Module for End-Stage Liver Disease; PV, peritoneovenous; TIPS, transjugular intrahepatic shunt



## Cirrhosis, Ascites and Surgery

- Postoperatively prevent reaccumulation of ascites
  - Dietary  $\text{Na}^+$  2 g/d
  - No / minimal IV fluids (use ↓  $\text{Na}^+$ -containing IV fluids)
  - Water intake po limited only if hyponatremia present
- Treatment
  - Abdominal binder
  - Standard treatment of ascites
  - laparoscopic repair of any associated hernia

## Refractory Ascites

- Definition
    - "...avoid overload that is non-responsive to  $\text{Na}^+$  restricted diet (2 g/d) plus spironolactone 400 mg/d and furosemide 160 mg/d, or
      - Recurs rapidly after therapeutic paracentesis
    - Serial LVP 6 – 8 L plus albumin 5 – 10 g/L ascites removed
      - TIPS
      - Peritoneus shunt
        - Indications
          - Not a candidate for LVP, TIPS or LT
- 
- Consider liver transplantation (LT)

Abbreviations: LT, liver transplantation; LVP, large volume paracentesis; TIPS, transjugular intrahepatic portosystemic shunt

## Cirrhosis Ascites or Cellulitis

- Definition
  - Soft tissue infection of abdominal wall +/- ankles
- Clinical
  - Pain / tenderness / erythema at site of infection
- Treatment
  - Antibiotics
    - Community-acquired
      - 1<sup>st</sup> generation cephalosporin
    - Hospital-acquired
      - 3<sup>rd</sup> generation cephalosporin, plus
      - Vancomycin (MRSA concern)
      - Cloxacillin
  - Avoid paracentesis over site of infected skin



## SPONTANEOUS BACTERIAL PERITONITIS (SBP)

### ➤ Definition

- Ascitic fluid neutrophil count  $\geq 250$  cells /mm<sup>3</sup> ( $0.25 \times 10^9$  /L) without an obvious intraabdominal, surgically treatable source of infection.
- Culture
  - Negative neutrocytic ascites
  - PMN  $\geq 250$  cells /mm<sup>3</sup> but negative culture of ascetic fluid
  - 2/3 culture-negative become culture-positive neutrocytic ascites
- Monomicrobial non-neutrocytic bacterascites
  - Culture-positive ascites but no  $\uparrow$  neutrophilic response (PMN  $< 250$  /mm<sup>3</sup>) ("bacterascites")

### ➤ Demography

- Outpatients ~2%
  - Inpatients ~10%
- } Cirrhosis with ascites plus SBP

- Give the clinical and laboratory characteristics of the cirrhotic patient who is suspected of having spontaneous bacterial peritonitis (SBP).

- Suspicion
  - Cirrhotic patient with new ascites,
  - Hospitalized cirrhotic, with / without localized / systemic infection
  - Abdominal pain / tenderness
  - Fever
  - Hepatic encephalopathy
  - $\uparrow$  hepatic / renal failure
  - $\downarrow$  total protein concentration in ascitic fluid ( $< 10$  g /L)
  - $\uparrow$  serum bilirubin
  - Peripheral leukocytosis\*
- Diagnostic paracentesis
  - Ascitic fluid characteristics compatible with SBP
  - Ascitic fluid PMN count  $\geq 250$  cells/mm<sup>3</sup>, or
  - Ascitic fluid bacterial culture-positive, plus
  - Absence of another source of infection, e.g., intra-abdominal or surgical
  - Ascitic fluid  $< 250$  cells/mm<sup>3</sup>, but abdominal pain / tenderness, and fever  $> 100$  °F

\* the PMN count in ascetic fluid does not correlate with the PMN count in the blood

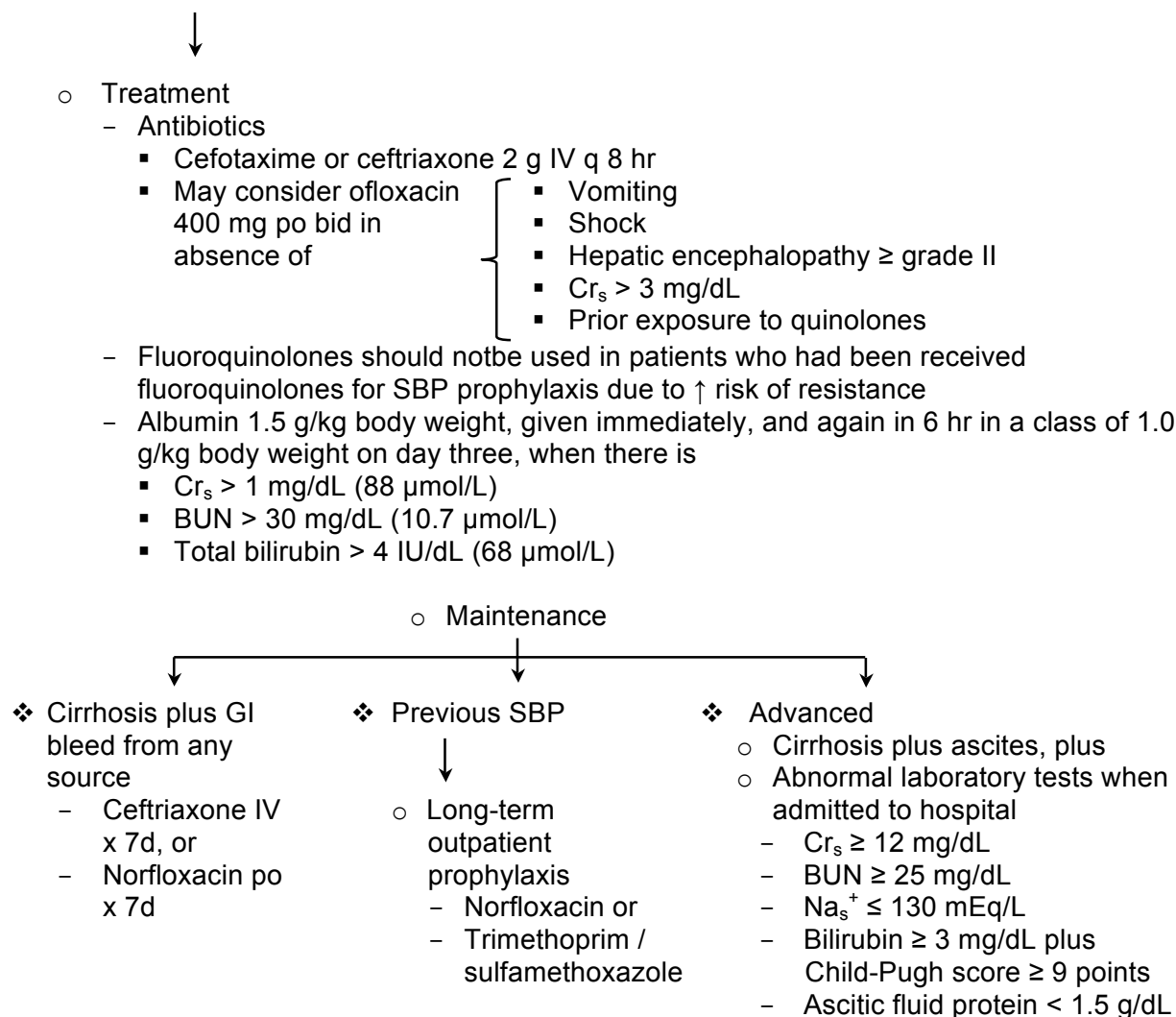
## SO YOU WANT TO BE A GASTROENTROLOGIST!

- Give the components of the intestinal barrier which may be altered by pre- / probiotics and might thereby reduce bacterial translocation from the intestinal tract, and thereby reduce the risk of bacterial infections.
  - $\uparrow$  tight junction proteins  $\rightarrow$   $\downarrow$  permeability across the epithelium
  - $\uparrow$  mucus secretion
  - $\uparrow$  sIgA (secretory IgA)
  - $\uparrow$  polymorphonuclear WBCs; neutrophils (PMNs)
  - $\downarrow$  inflammatory cytokines

}  $\uparrow$  innate immunity







Abbreviations: BUN, blood urea nitrogen; CCT, creatinine clearance test;  $Cr_s$ , serum creatinine; IV, intravenous;  $K_u^+$ , urine potassium concentration;  $Na_s^+$ , urine sodium concentration; PMN, polymorphonuclear cells; RBC, red blood cell count; WBC, white blood cell count

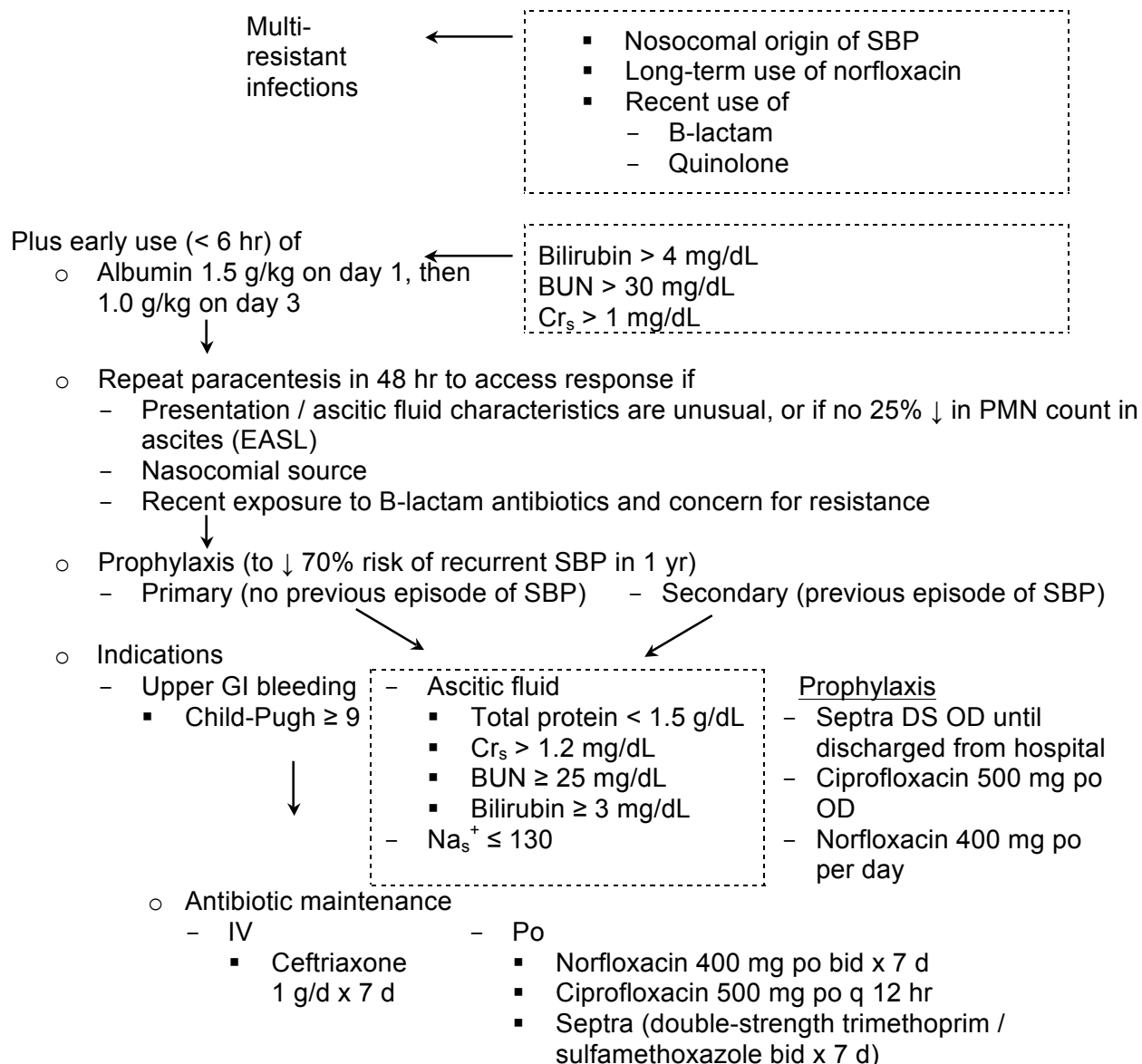
- Empiric antibiotics
  - Usual organisms
    - Escherichia coli
    - Klebsiella pneumoniae
    - Streptococcal pneumonia
    - B-lactamse-producing Enterobacteriaceae

- Cefotaxime 2 g IV q 8 hr, or
  - Ofloxacin 400 mg po bid x 8 d

SBP patients with no

- HE ( $\geq$  grade II)
- $Cr_s > 3$  mg/dL
- Vomiting
- Shock





Abbreviations: BUN, blood urea nitrogen; Cr<sub>s</sub>, serum creatinine; Na<sub>s</sub><sup>+</sup>, serum sodium concentration

#### Clinical Caution

- Exclude secondary peritonitis (free perforation, or loculated abscess) from SBP:
  - Multiple organisms (often including fungi and enterococcus on gram stain)
  - Biochemistry of ascitic fluid
    - Glucose < 50 mg/dL
    - Lactate dehydrogenase (LDH) > ULN for serum
    - Total protein > 1 g/dL
  - CT scan changes compatible with free perforation or abscess
    - Sensitivity 85% - Abscess for perforating, 50% for non-perforating



## HEPATORENAL SYNDROME (HRS)

### ➤ Definition

#### ❖ Short version

- Progressive reduction in renal function
    - 2x ↑ of the initial  $Cr_s$  to  $> 2.5$  mg/dL, or
    - 50% of the initial CrCl to  $< 20$  mL/min
- }  $< 2$  wk

#### ❖ Long version

- Above plus absence of
  - Recent / current use of nephrotoxic drugs
  - Proteinuria  $> 500$  mg/d
  - $> 50$  RBC per hpf
  - Abnormal renal ultrasound

Abbreviations: CrCl, creatinine clearance; hpf, high power field

- Suspicion of HRS



- $Cr_s$ 
  - $> 1.5$  mg/dL ( $> 133$   $\mu$ mol/L)
  - No change, or no ↓ to  $< 1.5$  mg/dL after
    - Stopping diuretics
    - Giving 1 g/kg albumin per dat, up to maximum of 10 g/d, or
    - Give albumin until CVP  $> 3$  cm water
- Absence of
  - Shock
  - Nephrotoxic drug use
  - Protein urea  $> 500$  mg/d
  - Hematuria  $> 50$  RBC/hpf
  - Abnormal renal ultrasound
- ↑ urinary neutrophil gelatinase-associated lipocain (UNGAL)

### ➤ Types

- I
  - Rapid progression
    - ↑  $Cr_s$
    - ↓ CC by 50%  $< 20$  mL/min in  $< 2$  wk
- II
  - Slow progression



➤ Treatment

- Correct frequently associated infection, such as spontaneous bacterial peritonitis (SBP) antibiotics plus albumin infusion



- Renal replacement therapy
  - Hemodialysis
  - Continuous venovenous hemodialysis
- Venoconstrictor
  - Octreotide 200 µg SC tid plus

- Probability of response

- Day 1 serum bilirubin < 10 mg/dL
- Day 3 MAP > 5 mm Hg

- Midodrine 12.5 mg po tid or
- Norepinephrine or terpressin 1 mg/q 4 – 6 hr, increasing up to 2 mg/q 4-6 hr to ↓ rs to < 1.5 mg/dL (133 µ mol/L)
  - ↑ MAP, uV, Na<sup>+</sup><sub>s</sub> (usually 14 d)

- Volume repletion
  - Albumin 10-20 g/d x 20 d

- No renal replacement therapy (RRT)



- Liver transplantation (survival rate, type I HRS, ~ 65%)

- Renal replacement therapy
  - Hemodialysis
  - Continuous venovenous hemodialysis > 8 wk RRT (must satisfy criteria for renal support)



Combined liver-kidney transplantation

➤ Prognosis

- Survival rate
 

|      |     |
|------|-----|
| 1 yr | 40% |
| 2 yr | 25% |
- Risk of recurrence of SBP at 1 yr 70%

Abbreviations: Hg, mercury; MAP, mean arterial pressure; Na<sup>+</sup><sub>s</sub>, serum sodium concentration; RRT, renal bacterial peritonitis; SBP, spontaneous bacterial peritonitis; uV, urine volume



## SPONTANEOUS BACTERIAL PLEURAL EMPYEMA / HYDROTHORAX

- Definition
  - Diagnostic thoracentesis showing
    - > 250 PMNs/mm<sup>3</sup> plus a positive culture, or
    - > 500 PMNs/mm<sup>3</sup> plus a negative culture
  - Hepatic hydrothorax
    - Hydrothorax in person with cirrhosis and ascites
    - Usually right-sided hemithorax effusion
- Demography
  - About 5% of persons with cirrhosis plus ascites develop hepatic hydrothorax
    - Of these, ~13% develop spontaneous bacterial pleural empyema
- Laboratory
  - Protein concentration in pleural fluid > ascetic protein concentration
  - ↑ neutrophil (polymorphonuclear white blood cells) count in fluid from hydrothorax
- Diagnostic Imaging
  - Technetium-radiolabelled sulfur colloid injected into ascites, and passes through defect in diaphragm
    - If suspicion of hepatic hydrothorax is high but scan is negative, repeat after large-volume thoracentesis
- Treatment
  - Similar management as SBP
  - TIPS
  - Pleurex catheter
  - Insertion of a chest tube is **contraindicated**

"A pessimist sees the difficulty in every opportunity;  
An optimist sees the opportunity in every difficulty."

Sir Winston Churchill



## PORTAL HYPERTENSION (PHT) AND CIRRHOSIS: NICE GUIDELINES

Abbreviation: NICE: National Institute of Health and Care Excellence

NICE guideline 2016. Cirrhosis in over 16s: assessment and management  
([nice.org.uk/guidance/ng50](https://www.nice.org.uk/guidance/ng50))

### ➤ Definition

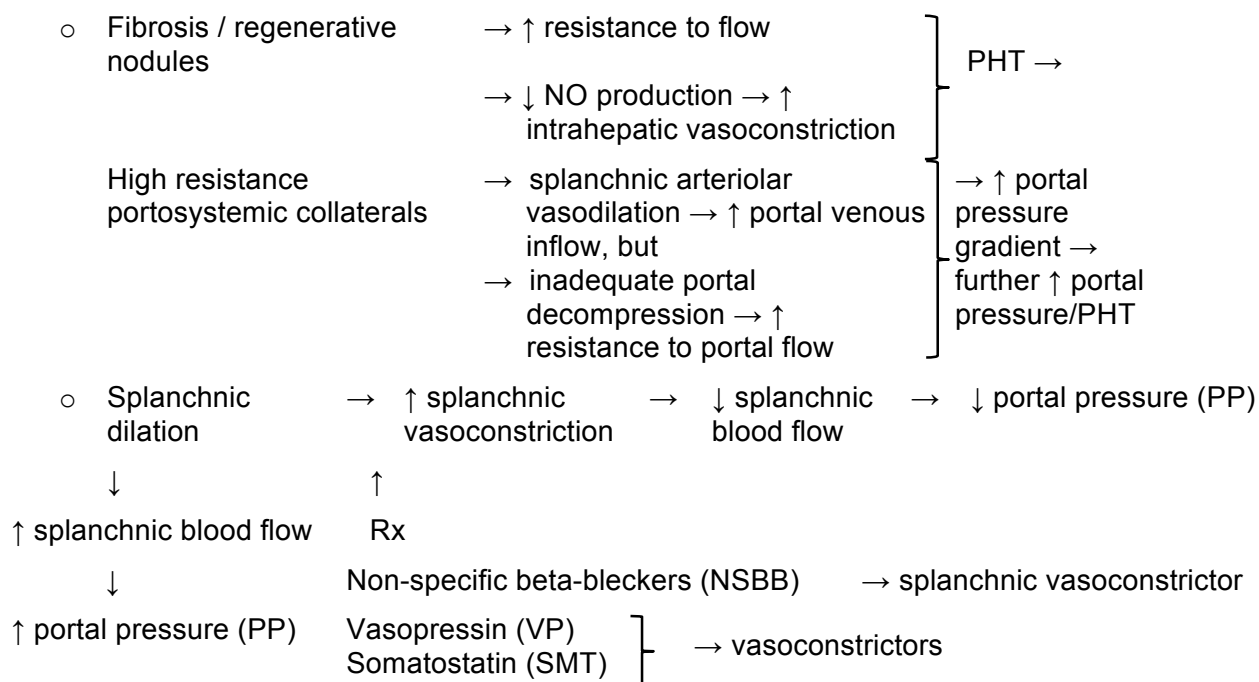
- Portal vein
  - Hepatic vein pressure (mm Hg; sinusoid pressure > 5 mm Hg)
  - Measured clinically as hepatic venous pressure gradient (HVPG)
    - Normal HVPG 3-5 mm Hg
    - WHVP – FHVP = HVPG

Abbreviations: FHVP, free hepatic venous pressure; WHVP; wedged hepatic venous pressure gradient

### ➤ Pathophysiology

- Portal pressure (PP)
  - Structural (70%)
    - Parenchyma
      - Fibrosis
      - Nodules (regenerative)
    - Vessels
      - Distortion
  - Functional (30%)

Endothelial dysfunction → ↑ NO → ↑ release of angiotensin-2, antidiuretic hormone, norepinephrine → intrahepatic vasoconstriction



- Give the reason why non-specific beta-blockers (NSBB rather than just B-1 adrenergic beta-blockers) are beneficial to treated portal hypertension.

|               | B-Adrenergic Blockade                                                                                    | Physiological Outcome                                                   |
|---------------|----------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------|
| - Nadolol     | <ul style="list-style-type: none"> <li>○ <math>\beta_1</math></li> <li>○ <math>\beta_2</math></li> </ul> | ▪ ↓ cardiac output                                                      |
| - Propranolol |                                                                                                          | ▪ Splanchnic vasoconstriction (unopposed $\alpha$ -adrenergic activity) |
| - Carvedilol  |                                                                                                          |                                                                         |

- Also has anti-  $\alpha_1$ -adrenergic → intrahepatic vasodilator
- Not recommended for secondary prophylaxis of recurrent gastric variceal bleeding (GVB)
- Give why NSBB are useful to treat clinically significant portal hypertension (CSPH), but not mild portal hypertension (PH).

| PH        | HVPG, mm Hg | HCS |
|-----------|-------------|-----|
| ○ Mild PH | > 5 to < 10 | -   |
| ○ CSPH    | ≥ 10        | +   |

Abbreviations: HCS, hyperdynamic circulatory state; HVPG, hepatic venous pressure gradient; PH, portal hypertension

- Give the treatment of gastric varices.
  - Treat any underlying condition, e.g., splenic portal vein thrombosis
  - EGD injection of cyanoacrylate glue (into gastric varices)
  - Balloon occluded retrograde transvenous obliteration (BRTO)
    - Sclerosants / liquid embolic agents injected through left renal vein → gastro- / splenorenal collateral
  - Transjugular intrahepatic portosystemic shunt (TIPS)

#### Clinical Pearls

##### ❖ Mortality Rates

- There is a predictive value of HVPG sinusoidal pressure, predicting when EGV will appear, and when EGV bleeding will occur.
- For each 1 mm Hg increase in the value of HVPG, there is a 3% ↑ mortality rate (MR in a median follow up period of 19 mon)
- EGVB develops when HVPG > 12 mm Hg, so the MR is ~ 36%



## SO YOU WANT TO BE A GASTROENTEROLOGIST!

HVPG measures hepatic sinusoidal pressure (normal, 3 -5 mm Hg).

- Give the pathophysiological subtype of portal hypertension in which measurement of HVPG, and therefore hepatic sinusoidal pressure, is useful.
  - Intrahepatic, portal hypertension and postsinusoidal sinusoidal obstruction syndrome (SOS)
  - The measurement of HVPG is used to assess portal hypertension (PH) in sinusoidal portal hypertension, such as that due to hepatic cirrhosis, as well as postsinusoidal SOS
- Give why the measurement of prehepatic PH in post-sinusoidal SOS, Budd-Chiari syndrome (BCS), and posthepatic PH, such as from right-sided heart failure (R-HF), is not clinically useful.

| Type of Portal Hypertension (site of<br>↑ resistance to blood flow) | HVPG                                                                                                  |
|---------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------|
| ○ Prehepatic; hepatic-presinusoidal                                 | N                                                                                                     |
| ○ Prehepatic, hepatic-<br>postsinusoidal, BCS                       | - Cannot pass obstructed HV to measure HVPG                                                           |
| ○ Post-hepatic right-sided heart<br>failure (R-HF)                  | - Both WHVP and FHVP are increased to the same amount, so<br>- HVPG is unchanged (HVPG = WHVP – FHVP) |

Abbreviation: BCS, Budd-Chiari syndrome

### ❖ Physical examination

- Physical examination may show signs which predict the presence of portal hypertension (PH) / cirrhosis (mild PH [HVPG > 5, < 10 mm Hg], clinically significant portal hypertension [CSPH; HVPG > 10 mm Hg])
- Note however that the cirrhosis-related physical findings does not indicate the absence of portal hypertension

### ➤ Laboratory and diagnosis imaging (non-invasive tests)

- Combination (LSP score)
  - ↓ platelets
  - Splenomegaly
  - ↑ liver stiffness (transient elastography [TE]; FibroScan®)
  - LSP score (LSPS)
 } Predictive of HVPG ≥ 12 mm Hg (EGV, CSPH)
   

$$\frac{\text{Liver stiffness, kPa} \times \text{spleen size, cm}}{\text{Platelet count (number per mm}^3\text{)}}$$
  - LSPS > 2.06 has PPV of > 90% for ruling in CSPH (HVPG = 10 mm Hg)
- Ultrasound, CT, MRI signs





- PV
  - ↑ diameter
  - ↓ flow velocity
  - Retrograde (reversal of flow)
- Portocollateral vessels
  - Recanalization
    - Paraumbilical vein
    - Splenorenal vein
    - Gastric veins (left and short)
- Transient elastography (TE; FibroScan®)
  - Liver stiffness > 20-25 kPa (kilopascals)
    - Diagnostic accuracy of CSPH > 90% [clinically significant portal hypertension, HVPG ≥ 10 mm Hg]
- Give non-invasive (non-endoscopic [EGD]) screening testing which may be used to screen a cirrhotic patient for possible EGV which may have features suggesting a high risk of future EGVB, and therefore the need for NSBB / EVL.
  - TE LS < 20 kPa
    - < 5% risk of high risk EGV
  - Platelet < 150,000/mm<sup>3</sup>

Abbreviations: EGV, esophagogastric varices; EGVB, esophagogastric variceal bleed; EVL, esophageal variceal ligation; NSBB, non-specific beta blockers; TE, transient elastography

#### Clinical Gem

- The identification of new portosystemic collaterals on physical examine (anterior abdominal wall, umbilical veins; Caput medusa), or other collaterals on diagnostic imaging (splenorenal, left/short gastric veins) suggests the development or progression of EGV.

#### ➤ Surveillance for EGV

- Compensated cirrhosis (CC, CACLD)
 

|                                                                                                                                                    | <u>EGD Frequency</u>                                           |
|----------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------|
| - No EGV <ul style="list-style-type: none"> <li>▪ Ongoing liver injury (alcohol, HBV / HCV, obesity)</li> <li>▪ No ongoing liver injury</li> </ul> | q 2 yr<br>q 3 yr                                               |
| - Small EGV <ul style="list-style-type: none"> <li>▪ Not candidates for primary prophylaxis</li> </ul>                                             | On going liver injury q 1 yr<br>No ongoing liver injury q 2 yr |
- Non-compensated cirrhosis (non CC)
  - EGD upon diagnosis of CC → non CC

Abbreviations: CACLD, compensated advanced chronic liver disease; CC, compensated cirrhosis; EGV, esophagogastric varices; HBV, hepatitis B infection; HCV, hepatitis C infection



➤ Treatment

❖ Primary prevention

- Compensated cirrhosis (CC; aka CACLD, compensated advanced chronic liver disease) plus mild portal hypertension (MPH)
- HVPG > 5 < 10 mm Hg; No EGv
- Treat underlying disease liver disease
- CC plus clinically significant portal hypertension (CSPH)
  - No EGv
    - Treat underlying liver disease
  - EGv, high risk of bleeding
    - Definition of high risk EGv
      - All decompensated patients with small / large varices
      - All compensated patients with
        - Varices with red wale signs
        - Large varices
    - NSBB to HR to 55 - 60 bpm (beats per min to ↓ HVPG to ≤ 12 mm Hg)
      - Outcomes
        - ↓ first EGVB                      - local benefit
        - ↓ ascites                                } - systemic benefit
        - ↓ mortality
- Large varices, high-risk small varices
  - NSBB2

| Name of NSBB  | Starting Dose,<br>then Change<br>Dose q 2-3 d to<br>Meet Target | Target   |           | Maximum Dose |         |
|---------------|-----------------------------------------------------------------|----------|-----------|--------------|---------|
|               |                                                                 | R-HR bpm | SBP mm Hg | No ascites   | Ascites |
| ▪ Propranolol | 20-40 mg po bid                                                 | 55-60    | < 90      | 320          | 160     |
| ▪ Nadolol     | 20-40 mg po od                                                  | 55-60    | < 90      | 160          | 80      |
| ▪ Carvedilol  | 6.25 mg po od                                                   | -        | < 90      | 12.5         |         |

- Esophageal variceal ligation (EVL), followed by surveillance EGD and possible EVL
  - Perform q 2-8 wk until eradication of esophageal varices, then q 3-6 mon for 1-2 yr, q 6-12 mon



### Child-Pugh Classification of the Severity of Cirrhosis

|                             | Points*      |                                       |                             |
|-----------------------------|--------------|---------------------------------------|-----------------------------|
|                             | 1            | 2                                     | 3                           |
| ○ Encephalopathy            | None         | Grade 1-2 (or precipitant-induced)    | Grade 3-4 (chronic)         |
| ○ Ascites                   | None         | Mild / Moderate (diuretic-responsive) | Tense (diuretic-refractory) |
| ○ Bilirubin (mg/dL)         | < 2          | 2-3                                   | > 3                         |
| ○ Albumin (g/dL)            | > 3.5        | 2.3-3.5                               | < 2.8                       |
| ○ PT (sec prolonged) or INR | < 4<br>< 1.7 | 4-6<br>1.7-2.3                        | > 6<br>> 2.3                |

\* 5-6 points: Child A; 7-9 points: Child B; 10-15 points: Child C.

Garcia-Tsao G, et al. Hepatology. 2007;46(3):922-38.

### Portal Hypertensive Bleeding In Cirrhosis: AASLD and NICE Guidelines

Abbreviations: AASLD, American Association for the Study of Liver Diseases; NICE, National Institute of Health and Care Excellence

AASLD Practice Guidance: Garcia-Tsao G, et al. Hepatology 2017; 65: 310-335

Also please see NICE guideline 2016. [www.nice.org.uk/guidance/ng50](http://www.nice.org.uk/guidance/ng50).

#### ➤ Demography

|                            | EGV   |                                          |
|----------------------------|-------|------------------------------------------|
| Compensated cirrhosis (CC) | ~ 1/3 | Develop ~ 7% per yr                      |
| Decompensated cirrhosis    | 85%   | Progress ~ 10% per yr<br>(small → large) |

- EGVB ~ 10% per yr
  - Mortality rate, 6 wk, ~ 20%
  - Recurrent (untreated) 60% within 2 yr of index EGVB

- Give the factors which ↑ risk of EGV bleeding (EGV → EGVB).
  - EGV
    - HVWP
    - Size
    - Red wale marks (thin wall of varix)
  - Patient
    - Alcohol
    - Obesity
  - Liver
    - Bacterial infection



## ➤ Definition

- Portal pressure gradient between portal vein and hepatic vein > 5 mm Hg
- Best determined by measuring WHVP (wedged hepatic venous pressure, a measure of sinusoidal pressure [SP]) and FHVP (free hepatic venous pressure)
- Compensated cirrhosis (CC) (CC = CACLD)

|                                                                            | Mild (40%)<br>HVPG > 5 but<br>< 10 mm Hg | CSPH (60%)<br>HVPG ≥ 10 but<br>< 12 mm Hg |
|----------------------------------------------------------------------------|------------------------------------------|-------------------------------------------|
| - Asymptomatic                                                             | +                                        | +                                         |
| - Gastroesophageal varices (GEV)                                           | -                                        | -/+ (2 subtypes)                          |
| - Variceal hemorrhage                                                      | -                                        | +                                         |
| - Hepatic encephalopathy (HE)                                              | -                                        | +                                         |
| - Ascites                                                                  | -                                        | +                                         |
| - Hepatocellular cancer (HCC)                                              |                                          | +                                         |
| - Therapeutic aim: prevent VH<br>(decompensation), avoid alcohol / obesity | +                                        | +                                         |
| - Normal cardiac index (no hyperdynamic state)                             | +                                        | -                                         |

## Clinical Pearl

## Predictors of decompensation of cirrhosis

- HVPG (hepatic venous pressure gradient)
- ↑ MELD (Model for end-stage liver disease)
- ↓ albumin

## ➤ Staging

- Compensated cirrhosis (CC)
  - Mild portal hypertension (PH)
  - CSPH
- Decompensated cirrhosis
  - VH
  - HG
  - Ascites
    - Hepatorenal syndrome (HRS)
    - HF (HE plus jaundice)

## ➤ Classification

- Cirrhosis
  - Compensated advanced chronic liver disease (CACLB); aka compensated cirrhosis (CC)

| CTP class | Median survival, yr |
|-----------|---------------------|
| A         | > 12                |
| B / C     | 1.8                 |



- Decompensated
  - Ascites
  - Hepatic encephalopathy (HE)
  - Variceal bleeding (VB)
- Mild portal hypertension (PH), HVPG > 5, < 10 mm Hg
- Clinically significant PH (CSPH), HVPG ≥ 10 mm Hg
  - ↑ risk of EGV / VB, ascites, HE, HCC, postsurgical decompensation

- Compensated cirrhosis
    - Mild PH
    - Clinically significant portal hypertension (CSPH)
    - +/- EGV

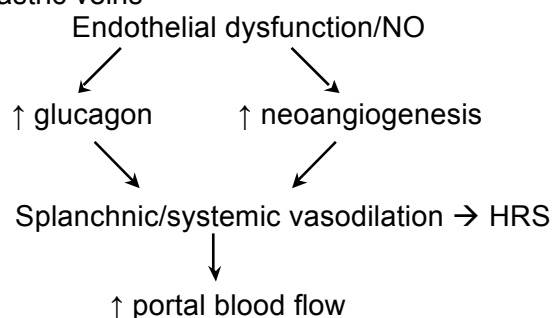
- Hepatic venous pressure gradient (HVPG)

|                                                                                    | mm Hg     | HCS |
|------------------------------------------------------------------------------------|-----------|-----|
| - Normal                                                                           | 3-5       | -   |
| - Mild PH                                                                          | > 5, < 10 | -   |
| - CSPH (EGV)                                                                       | ≥ 10      | +   |
| - EGVB                                                                             | ≥ 12      | +   |
| - High rate failure to control EGVB early rebleeding from EGV, high mortality rate | > 20      |     |

- When HVPG < 10 mm Hg
  - ↓ further to prevent development of CSPH (HVPG ≥ 10 mm Hg)
  - ↓ decompensation EGV → EGVB
- When HVPG ≥ 12 and EGV → EGVB
  - Control acute rebleeding
  - Prevent
    - Other complications
    - Need for liver transplantation (LT)
    - Death

#### The Magic of "10"

- When HVPG > 10 mm Hg collaterals develop between portal and systemic circulation
  - Coronary
  - Short gastric veins



- CACLD
  - Before cirrhosis is diagnosed histopathologically, there may be efficiently  $\uparrow$  HVPG to cause complications such as ascites, HE, VB
- Give an example of the prognostic value of CSPH.
  - Patients with CLD who have EGV have CSPH with HVPG > 10 mm Hg
 

|                                     | <u>5 yr Mortality Rate</u> |
|-------------------------------------|----------------------------|
| - Cirrhosis plus EGV                | 20%                        |
| - EGV + other hepatic complications | 80%                        |

Abbreviations: AASLD, American Association for the Study of Liver Diseases; CACLD, compensated advanced chronic liver disease; CC, compensated cirrhosis; CSPH, clinically significant portal hypertension; EGV, esophagogastric varices; EGVB, esophagogastric variceal bleed; HCS, hyperdynamic circulatory state; PH, portal hypertension; PP, portal pressure

### SO YOU WANT TO BE A GASTROENTEROLOGIST!

- Give the adverse effects of obesity ( $\uparrow$  BMI) and alcohol consumption on the prognosis of patients with cirrhosis.
  - $\uparrow$  fibrosis
    - $\uparrow$  decompensation
    - $\downarrow$  regression (viral cirrhosis)
  - Alcohol
    - $\uparrow$  portal pressure (PP)
    - $\downarrow$  prognosis (HCV-, NASH+ associated cirrhosis)

### ➤ Prognosis

- Recurrent VH, HE
- Refractory ascites
- $\downarrow$   $\text{Na}_s^+$ 
  - $\downarrow$
- Cirrhosis
 

|                 | <u>Medial Survival, yr</u> |
|-----------------|----------------------------|
| - Compensated   | 12                         |
| - Decompensated | 1.8                        |
- Treatability of underlying liver disease (independent prognostic factors)
- Associated
  - Use of alcohol
  - Obesity
- Variceal hemorrhage (VH)
 

|                           | <u>5 yr Mortality</u> |
|---------------------------|-----------------------|
| - Isolated complication   | 20%                   |
| - Associated complication | 80%                   |

Abbreviations: ALF, advanced liver fibrosis; CACLD, compensated advanced chronic liver disease; CSPH, clinically significant portal hypertension; GEV, gastroesophageal varices; HCC, hepatocellular carcinoma; HE, hepatic encephalopathy; HF, hepatic failure; HRS, hepatorenal syndrome; HVPG, hepatic vein pressure gradient;  $\downarrow$   $\text{Na}_s^+$ , hyponatremia (low serum sodium concentration); VH, variceal hemorrhage



## ACUTE ESOPHAGEAL AND GASTRIC VARICEAL (EV, GV) BLEEDING

### ➤ Demography

- Annual rate of development of variceal bleeding, 8%
- Annual rate of progression of small (< 5 mm, minimal elevation above mucosal surface of esophagus) to large (> 5 mm, > 1/3 of lumen of esophagus) EV, 8%
- Give factors which predict the ↑ risk of small varices progressing to large.
  - Cause – Alcoholic cirrhosis
  - Function – Child-Pugh B / C (decompensated cirrhosis)
  - EGD – Red wale marks\*
  - Presence of esophageal varices (EV)
    - At time of diagnosis of cirrhosis, 30%
    - Bleeding within first yr of diagnosis of cirrhosis, 30%
    - In patients with 10 yr of known cirrhosis, 90%
  - Annual rate of variceal bleeding ~ 10%
    - Point prevalence of medium / large varices, ~20%
  - Risk of rebleeding, 80%
  - Mortality from any EV bleeding
    - Child-Pugh
      - A, < 10%
      - C, > 70%

### MCQ Alert

Half (50%) of patients with cirrhosis have esophageal varices (EV).

- Give precirrhotic or non-cirrhotic conditions in which EV develop.
  - Alcoholic hepatitis (transient elevation in PP)
  - Primary biliary cirrhosis (PBC)
  - HCV with bridging fibrosis
  - Presinusoidal portal hypertension
  - Acute onset of liver failure

### ➤ Measurements

- Wedge hepatic venous pressure (WHVP) minus effect of ascites
  - Free hepatic vein pressure (FHVP), or
  - Intraabdominal IVC pressure (IVCP)

→ Hepatic venous pressure gradient (HVPG)



$$\text{HVPG} = \text{WHVP} - \text{FHVP} / \text{IVCP}$$

○ Significance of HVPG measurements (mm Hg)

- Normal 3.5
- Varices
  - Form > 10
  - Bleed from EV > 12
- Complication
  - Failure to stop bleeding } > 20
  - Early rebleeding ↑ mortality rate at 1 yr (64% vs 20%)

MCQ Trick

- Give the mechanism of action of non-specific beta blockers in reducing the risk of bleeding from esophageal varices.
  - NSBB → ↓ portal venous, flow, resistance on pressure → ↓ EV bleeding

Abbreviations: EV, esophageal varices; IVC, inferior vena cava

➤ Treatment

❖ Principles of pharmacotherapy in bleeding EV

| Pathophysiology | Pharmacophysiology<br>Mechanism of Action                      | Portal |            |                                         |
|-----------------|----------------------------------------------------------------|--------|------------|-----------------------------------------|
|                 |                                                                | Flow   | Resistance | Pressure                                |
| ○ ↑ inflow      | - Splanchnic vasoconstriction                                  | ↓↓     | ↑          | ↓                                       |
| ○ ↑ resistance  | - Venodilation (↓ intrahepatic +/- portocollateral resistance) | ↓      | ↓          | ↓ (↓ portal pressure, as well as ↓ MAP) |
|                 | - Shunt DSRS / TIPS                                            | ↑      | ↓↓↓        | ↓↓↓                                     |

Abbreviations: DSRS, distal splenorenal shunt; MAP, mean arterial pressure; TIPS, transjugular intrahepatic portosystemic shunt

- Give the benefits of therapeutically reducing HVPG to < 12 mm Hg.
  - ↓ risk of
    - Rebleeding EV
    - Formation of ascites
    - Development of spontaneous bacterial peritonitis (SBP)
    - Death

➤ Prognosis of bleeding EV

- 6 wk mortality, > 20%
- Late rebleeding (1-2 yr after first EV bleed), 60%

➤ Surveillance EGDs for EV / GV

- Initial screening EGD
  - At diagnosis cirrhosis
  - No varices q 3 yr (2-3)
  - Small varices q 2 yr (1-2)
- Decompensated cirrhosis q 1 yr





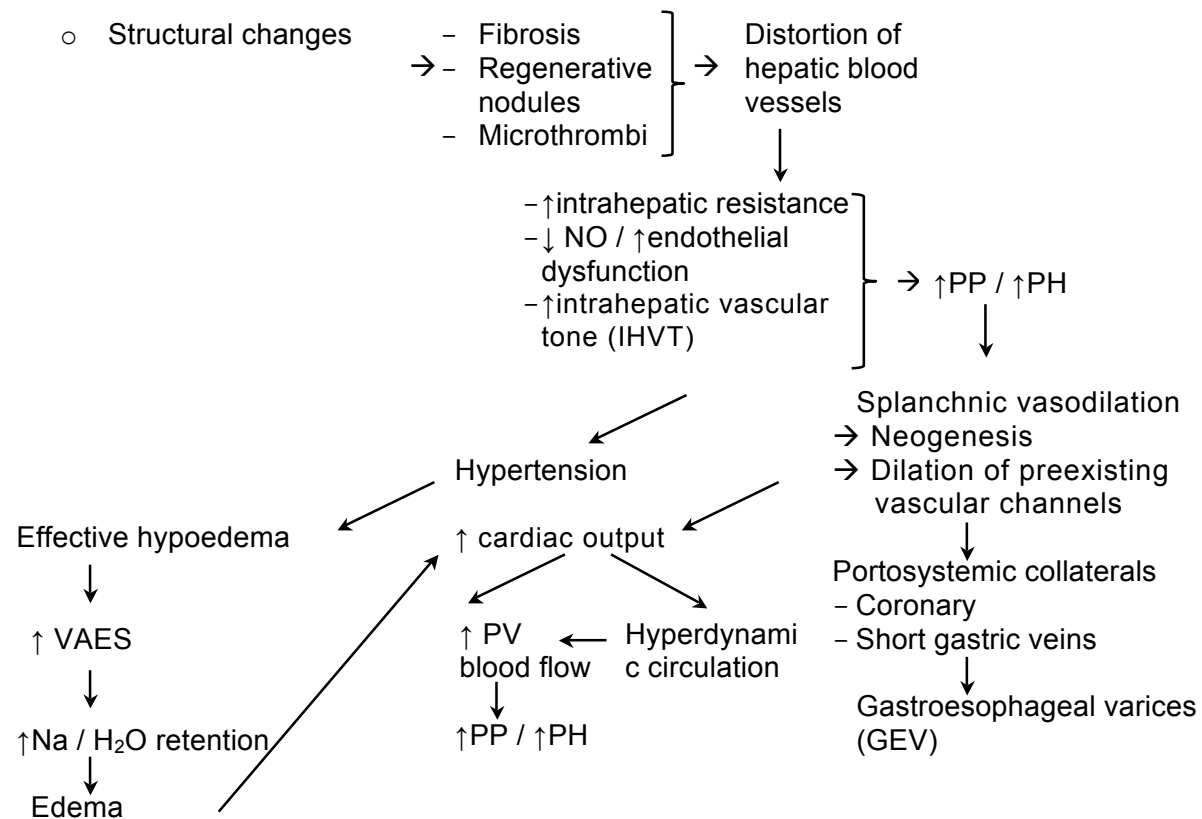
## GASTROESOPHAGEAL VARICES (GEV)

### ➤ Demography

- Compensated cirrhosis (CC) – CTP-A ~ 40%
- Decompensated cirrhosis (VH, HE, ascites) – CTP-B / C ~ 80%
- Development of GEV – ~ 8% per yr
- Progression of GEV small → large – ~ 12% per yr
- Risk of VH from GEV – ~10% per yr
  - Depends upon presence of GEV
    - Size
    - Red wale marks
      - HVPG > 20 mm Hg
      - Bacterial infection
- 6-wk mortality of VH – 20%

### ➤ Pathophysiology

Note: An understanding of the pathophysiology of portal hypertensive (PH) is essential for the clinician to understand the subtiles of management of PH and its complications.



Abbreviations: HE, hepatic encephalopathy; NO, nitric oxide; PH, portal hypertension; PP, portal pressure; VAES, vasoactive enzyme systems; VH, variceal hemorrhage



- Give the pathophysiology and implications of the presence of gastroesophageal varices (GEV).

$$\text{HVP} = \text{WHVP} - \text{FHVP}$$

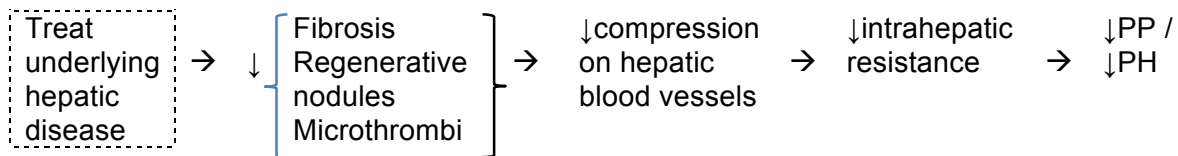
- GEV from when HVP  $\geq 10$  mm Hg
  - Continued  $\uparrow$  HVWP to  $> 12$  mm Hg  $\rightarrow \uparrow$  risk of VH (variceal hemorrhage)
- HVWP  $> 12$  mm is called CSPH (clinically significant portal hypertension), and is associated with  $\uparrow$  risk of VH from GEV
  - Hepatic encephalopathy (HE)
  - Ascites
  - Post-surgical hepatic decompensation
  - Hepatocellular carcinoma (HCC)

Abbreviations: GEV, gastroesophageal varices; VH, variceal hemorrhage

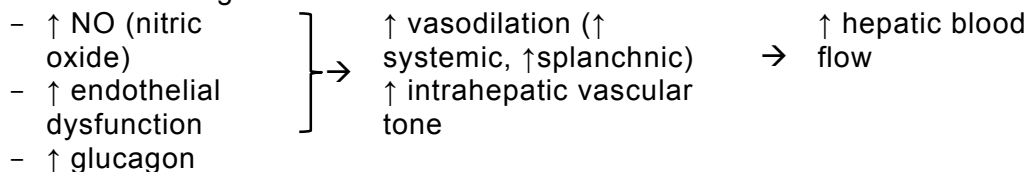
- Give the use of HVP to predict the prognosis of the patient with cirrhosis and portal hypertension.

1 mm Hg  $\uparrow$  in HVP  $\rightarrow 3\%$   $\uparrow$  risk of death within 19 mon

- Structural changes



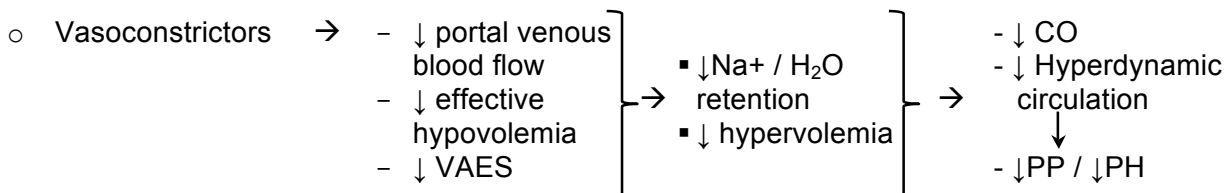
- Functional changes



- Carvedilol
- Statins

- Collaterals, shunts, splanchnic vasodilation





- NSBB (B2-adrenergic blocking effect)
- Somatostatin
- Vasopressin

- Systemic vasodilation → effective hypovolemia → ↑VAES → ↑Na<sup>+</sup> / H<sub>2</sub>O retention → Effective hypovolemia → ↑ cardiac output → hyperdynamic circulation → ↑ portal venous blood flow

- TIPS - ↓ hepatic resistance
- EBL, BRTO - Stop VH from GEV

Abbreviations: BRTO, balloon occluded retrograde transvenous obliterations; CO, carbon monoxide; EBL, endoscopic band ligation; GEV, gastroesophageal varices; Na<sup>+</sup>, sodium; NO, nitric oxide; NSBB, non-selective beta blocker; PH, portal hypertension; PP, portal pressure; TIPS, transjugular intrahepatic portosystemic shunt; VAES, vasoactive enzyme system

#### More MCQs and Pharmacology

- Give why carvedilol has properties which make it a unique NSBB to use to improve the functional component of ↑ hepatic resistance, while still having use to treat the systemic vasodilation leading to the activation of the vasoactive enzyme systems (VAES) and the hyperdynamic circulation which results from ↑ cardiac output and ↑ portal venous blood flow.
  - Carvedilol is a vasodilator of the systemic as well as the intrahepatic circulation. Its anti-α<sub>1</sub> adrenergic → ↓ portal flow (↓ MAP [mean antral pressure]) its NSBB attributes have a vasodilator effect on the intrahepatic circulation → ↓ HVPG.
- Give the reason why NSBB are not indicated in person with compensated cirrhosis (CC) with mild portal hypertension (HVWP > 5 but < 10 mm Hg).
  - These patients have no ↑ Cs (↑ cardiac output index), and as well they have normal cardiac index, no ↑ portal venous inflow, and no ↑ portal pressure from these functional changes.
- Give the mechanisms of the benefit of statins for patients with cirrhosis with portal hypertension.
  - Antifibrotic properties
  - ↑ endothelial function
  - Intrahepatic vasodilation → ↑ hepatic blood flow  
↑ hepatic function



### MCQ and Pharmacology in Cirrhosis / Portal Hypertension

- Give why the splanchnic vasoconstrictors (NSBB, VP, SMJ) do not improve hepatic function in the cirrhotic patient with portal hypertension.
  - Other vasoconstrictors decrease the splanchnic blood flow and reduce portal pressure so ↓ risk of GEV turning into VH.
  - However, the ↓ blood flow from this vasoconstriction results in ↓ blood flow to the remaining hepatocytes, potentially impairing any improvement in liver function.
- Give why only the non-specific beta blockers (NSBB) are recommended to be used to treat portal hypertension.
  - There are  $\alpha$ - and  $\beta$ -adrenergic receptors, and the  $\beta$ -adrenergic blockers subtypes are  $\beta_1$  and  $\beta_2$ .
  - Blocking  $\beta_1$  receptors → ↓ heart rate (HR) → ↓ cardiac output CO
  - Blocking  $\beta_2$  receptors leaves unopposed  $\alpha$ -adrenergic activity
  - The unopposed  $\alpha$ -adrenergic activity causes the desired splanchnic vasoconstriction as well as the ↓ CO / ↓ hyperdynamic circulation, and this reduces the increased hepatic venous inflow and thus decreases portal pressure and portal hypertension
- Give the adverse effects of angiotensin-2 blockers (ACIs, ARBs) in persons with cirrhosis and portal hypertension.
  - ↑ systemic vasodilation
    - ↓ systemic blood pressure
    - ↑ Na<sup>+</sup> retention
    - ↑ risk of or worsening of ascites

Abbreviations: CO, cardiac output; NSBB, non-specific beta-blockers

### Therapeutic TIP

- There is no risk for the use of NSBB in persons with compensated cirrhosis (CC) and mild portal hypertension (portal pressure [PP], HVWP > 5 but < 10 mm Hg).



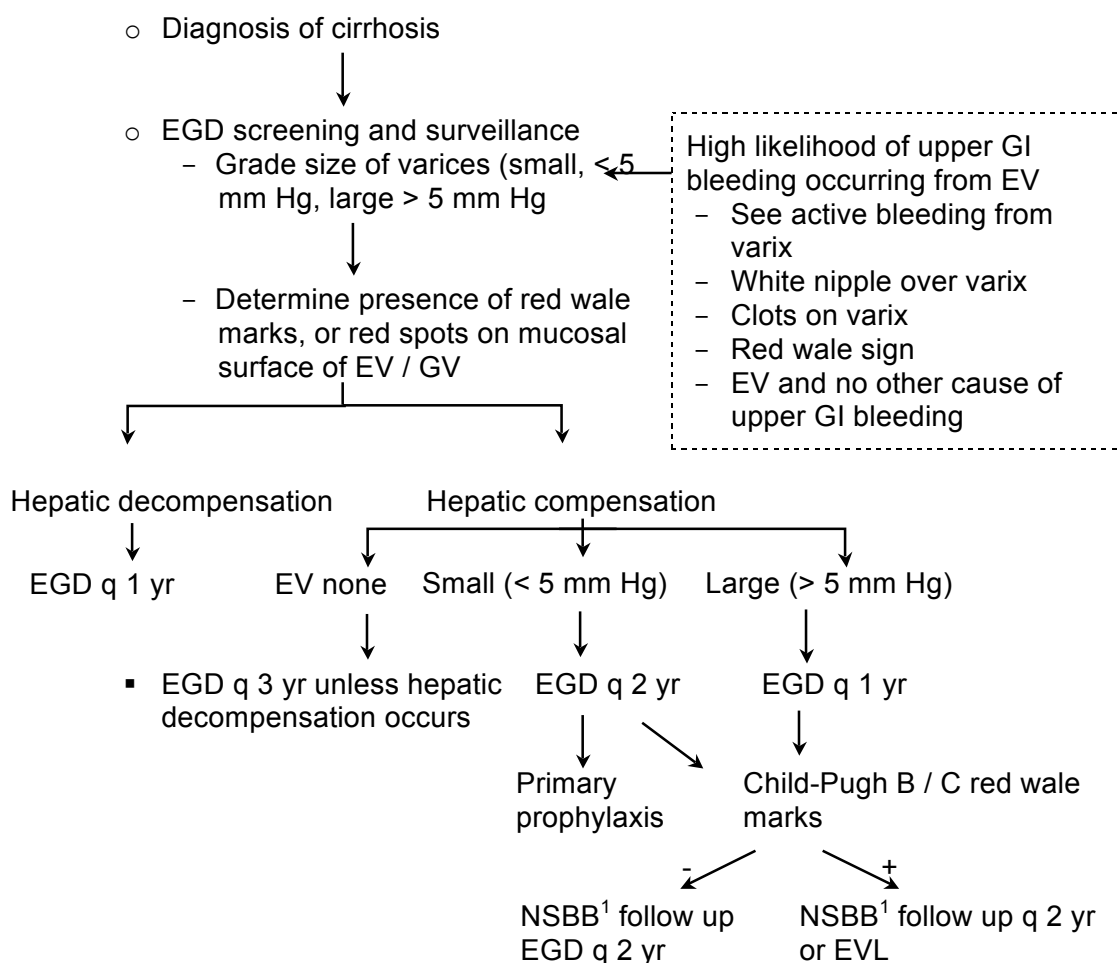
## Gastroesophageal Variceal Hemorrhage in Cirrhosis AASLD / WGO Guidelines

Abbreviations: AASLD, American Association for the Study of Liver Diseases; WGO, World Gastroenterology Organization

AASLD / ACG: Garcia-Tsao G, et al. Hepatology 2007; 46: 922-938; AASLD: Garcia-Tsao G, et al. Hepatology 2017; 65: 310-335; WGO World Gastroenterology Organization 2014.

Also please see Garcia-Tsao G and Bosch J. N Engl J Med 2010; 362: 823-832.

### ❖ Primary Prophylaxis of EV



<sup>1</sup> The dose of NSBB (propranolol, nadolol, carvediol) should be adjusted to the maximal tolerated dose, not just to pulse rate < 60 bpm, or 20% over baseline, e.g., nadolol 40 mg po od or propranolol 20 mg po bid, as starting doses

- The beta blocker used must be non-specific, with both B-1 effect to ↓ cardiac output, and B-2 effect to ↓ portal flow

<sup>2</sup> EVL at time 0, then q 1-2 wk until EV obliterated, then 1-3 mon, then q 6-12 mon

- EBL / sclerotherapy stops EV bleeding in 90%



- Non-specific B blockers (NSBB) may be used for primary and secondary prophylaxis of bleeding esophageal varices in compensated or decompensated cirrhosis plus small or large varices. Give examples of when EVL might be preferable to NSBB in the patient with Child-Pugh B / C and red wale marks on small or large varices.
  - Non-adherence to NSBBs
  - Adverse effects to NSBBs
  - Failure if prophylaxis of EV bleeding
    - Dyspnea
    - Fatigue
    - Light headedness
    - Contraindications
    - NSBB
    - Asthma
    - Peripheral vascular disease

#### ❖ Acute Bleeding form EV

##### Clinical Pearl

- The cirrhotic patient with a Child-Turcotte-Pugh classification "C" often (80%) have an HVPG  $\geq 20$  mm Hg, and therefore a high risk of EVB.

- Consider airway protection (tracheal intubation)
- Stop NSBB (used for prevention of EV bleed)

- Antibiotics
  - All causes of GI bleeding
  - Even without presence of ascites

↓ bacterial infection  
↓ rebleeding  
↓ mortality rate

Ceftriaxone IV 1 g/d

Norfloxacin 400 mg po bid

Ciprofloxacin

For 7 d

- ABCs
- IV fluids
- PRBC to 7 g/dL, and maintain at 7-9 g/dL
- Octreotide
  - ↓ infection
  - ↓ bleeding
  - ↓ mortality
  - 50 mg IV bolus
    - Continues infusion 50 µg/hr for 2-5 days
  - Benefits
    - ↓ bleeding
    - ↓ RBC transfusions
    - ↓ mortality



- Other options (not to be added to octreotide)
    - Vasopressin
      - 0.2 – 0.4 U/min IV continuously – ↑ dose as needed to max 0.8 U/min, for 24 hr
      - Nitroglycerine 40 µg/min IV – ↑ dose as needed to max to 400 µg/min IV, for 24 hr
    - Somatostatin
    - Terlipressin
  - EGD when patient sufficiently stable, and always within 12 hr
    - Successful EGBL, plus CTP class C cirrhosis, or CTP-B with bleeding
 

↓

Early “preemptive” covered TIPS stent

↓

}

Balloon bridging  
tamponade

- EGVB stops 80%
      - Patient dies 20%
      - Remove balloon in 24 hr
      - Remove TIPS stent in < 7 d
  - Unless TIPS performed, stop octreotide in 2-5 d, and start NSBB
  - Octreotide 50 mcg IV bolus, then 50 mcg /hr for 5 d
    - Vasopressin      ▪ 0.2-0.4 U/min, increasing to 0.84 U/min if no adverse effects (AEs) continue for 5 d
    - Or
    - Terlipressin      ▪ 2 mg IV q 4 hr until bleeding controlled, then continue 1 mg IV q 4 hr once bleeding controlled
    - Plus
    - Nitroglycerin 40 mcg /min, increasing to 400 mcg/min until SBP > 90 mm Hg

↓  
 Early EGD (within 12 hr) for EBL  
 ↓  
 Failure or early rebleeding (in 10-20%)
- | Adverse effects of vasopressin |            |
|--------------------------------|------------|
| ○ Ischemia                     | Heart,     |
| ○ Arrhythmia                   | peripheral |
| ○ Hypertension                 | bowel      |
- Non-specific beta blockers (NSBB) are used to ↓ risk of primary or secondary EV bleeding. Give the reason NSBB are temporarily stopped in person with acutely bleeding EV.
    - NSBB such as propranolol or nadolol are useful for prevention of EV bleeding because of their B2 effect to cause splanchnic vasodilation and to thereby reduce the increased portal blood flow.
    - However, the B1 effect of NSBBs is to ↓ cardiac output, which would not be good in a patient with an upper GI bleed, such as from EV.

Abbreviations: ABC, airway breathing circulation; EBL, endoscopic band ligation; EGD, esophagogastroduodenoscopy; PRBC, packed red blood cells; SBP, systolic blood pressure

#### Rescue therapy

- Repeat therapeutic endoscopy (EVL)
- Shunt
- TIPS placement
  - Distal splenorenal shunt (DSRS)
- In patient with uncontrollable bleeding, may consider temporary use of balloon tamponade of TIPS / repeat EVL planned within 24 hr



Continued bleeding

Access for liver transplantation if  
MELD score ≥ 15; Child-Pugh score ≥ 7



- Give the mechanism of action of endoscopic band ligation (EBL) and esophageal sclerotherapy (EST) in reducing the risk of bleeding from esophageal varices (EV).
  - Local therapy to EV such as EBL or EST do not affect portal flow, resistance or pressure, but instead simply obstruct vessels responsible for bleeding, without altering variceal wall tension, vessel diameter, or pressure in the lumen of the varices.

#### Therapeutic caution

- Give the reason why balloon tamponade of the esophagus may be used in persons with uncontrolled bleeding esophageal varices despite use of octreotide, antibiotics and EBL, yet despite its success rate of 80% to control previously uncontrollable bleeding, the balloon tamponade must not be used for > 24 hr
  - The use of balloon tamponade is a life-saving therapy that must not be used for longer than 24 hr because of the 20% risk of lethal complications
    - Aspiration
    - Migration
    - Pressure necrosis/perforation

#### Treatment Tip

- Sometimes EBL is not sufficient to stop severe EV bleeding, and then preferring sclerotherapy may be successful. This is not standard of care in non life-threatening situations; EBL + sclerotherapy ↑ risk of esophageal stricture.

#### ❖ Secondary Prophylaxis

NSBB plus PPI



Risk of rebleeding ~ 35%

Pantoprazole 40 mg IV after EVL, then 40 mg po od X 9 d

- EVL q 1-2 wk until obliteration,
  - then at 1-3 mon, then q 6-12 mon, plus
- Protein pump inhibitor (PPI), plus
  - NSBB (follow up EGD q 2 yr)

Reduction of risk of rebleeding to ~ 35% without secondary prevention, risk of rebleeding and mortality rate is 33% and 60-80%

↓ Further bleeding

TIP or DSRS assessment for liver transplantation

#### Trick MCQ

- Give the advantage of EVL versus NSBB on mortality rate in EV bleeding.
  - EVL is superior to NSBB in ↓ bleeding episodes and to ↓ adverse effects, but there is no difference in mortality rate.





## GASTRIC VARICES (GV)

### ➤ Demography

- Present in ~ 20% of persons with cirrhosis
- Risk of bleeding 25% in 2 yr

### ➤ Buzz word associations

- GOV1 (type 1)
  - As an extension of EV, the treatment is similar to EV
- GOV2 (type 2 GV), IGV1 subtype
  - Think about possible etiology of splenic vein thrombosis (SVT)

### Trick Question

- The factors which predict an ↑ risk of bleeding esophageal varices is their size, the function of the patient's liver (Child-Pugh B/C) and the presence of red wale marks.
- The risk factors for bleeding gastric varices is also their size and the patient's Child-Pugh status, but an endoscopic feature different from red wale spots seen in EV.
- Give the EGD feature which represents a risk factor for bleeding gastric varices.
  - Red spots or red areas of mucosa over the varix/varices

### ➤ Types

- EV + GV
  - Lesser cure GOV1
  - Greater cure GOV2
- Isolated GV
  - Fundus IGV1
  - Other parts of stomach IGV2

### ➤ Classification, Sarin

|                              | Sites          | Extending Into       |                                            |
|------------------------------|----------------|----------------------|--------------------------------------------|
| ○ GOV1 (75%)                 | EV + GV        | Lesser curve         | } "Cardiofundal" – thrombosis of PV +/- SV |
| ○ GOV2                       | EV + GV        | Fundus               |                                            |
| ○ IGV1                       | GV             | Fundus               |                                            |
| ○ IGV2                       | GV             | Other than in fundus |                                            |
| ○ Risk of bleeding           |                |                      |                                            |
| – Site: IGV1 > GOV2 > GOV1   |                |                      |                                            |
| ▪ GV fundus                  | GV fundus + EV | GV lesser curve + EV |                                            |
| – Size                       |                |                      |                                            |
| – Red wales                  |                |                      |                                            |
| – Liver dysfunction severity |                |                      |                                            |

Abbreviations: GV, gastric varices; PV, portal vein; SV, splenic vein



➤ Risk of bleeding

- Varices
  - Site IGV1 > GOV2 > GOV1
  - Size large
  - Red wales
- Patient
  - Severe liver dysfunction

Abbreviations: EV, esophageal varices; GOV1 / GOV2, gastroesophageal varices; GV, gastric varices; IGV1 / IGV2, intragastric varices

➤ Treatment

- Gastric variceal obturation (GVO)
  - Injection with
    - N-butyl-cyanoacrylate
    - Isobutyl-2-cyanoacrylate
    - Thrombin
  - ↓ If GVO not available
  - EVL, or TIPS

❖ Primary prophylaxis

- GOV1 / GOV2, IGV1
  - NSBB

❖ Acute bleeding

|              | Acute Treatment                                                                                                                                                                | Secondary Prophylaxis                                                                       |
|--------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------|
| ○ GOV1       | <ul style="list-style-type: none"> <li>- EVL</li> <li>- Cyanoacrylate glue injection*</li> </ul>                                                                               | <ul style="list-style-type: none"> <li>▪ EVL</li> <li>▪ Cyanoacrylate injection*</li> </ul> |
| ○ GOV2, IGV1 | <ul style="list-style-type: none"> <li>- Transjugular intrahepatic portosystemic shunt (TIPS)</li> <li>- Balloon occluded retrograde transunous obliteration (BRTO)</li> </ul> |                                                                                             |
|              | ↓                                                                                                                                                                              |                                                                                             |
|              | Cyanoacrylate injection                                                                                                                                                        |                                                                                             |

- Rate of rebleeding may be lower with injection of cyanoacrylate than with EVL

Doppler ultrasound may be useful to demonstrate portal vein or splenic vein thrombosis.

- Give why Doppler ultrasound may help in the selection of therapy for patients with gastric varices.

- |                           |               |                                          |
|---------------------------|---------------|------------------------------------------|
| ○ Portal vein thrombosis  | - GOV1 / GOV2 | } GOV2 and IGV1 may be treated with TIPS |
| ○ Splenic vein thrombosis | - IGV1        |                                          |

❖ Primary prevention of first bleeding from gastric varices

- |                        |                                                                                                                                                                                                                                                                                                                                                                              |                                                                                                                                                                                                                                                     |
|------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| ○ Cardiofundal varices | <div style="display: inline-block; vertical-align: middle;"> <div style="font-size: 3em; vertical-align: middle;">{</div> <div style="display: inline-block; vertical-align: middle;"> <ul style="list-style-type: none"> <li>- IGV1 (Isolated gastric varices [GV] in fundus)</li> <li>- GOV2 (isolated GV in fundus plus esophageal varices [EV])</li> </ul> </div> </div> | <div style="display: inline-block; vertical-align: middle;"> <div style="font-size: 3em; vertical-align: middle;">}</div> <div style="display: inline-block; vertical-align: middle;"> <p>Large gastro- / splenorenal collaterals</p> </div> </div> |
|------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|



- Give why cross-sectional vascular imaging is performed in persons with gastric varices in the fundus +/- esophagus.
  - Cardiofundal varices may be associated with large gastro- or splenorenal collaterals / thrombosis
    - The management might be best directed at the vascular collaterals / thrombosis, rather at the fundal GV +/- EV
  - Glue (cyanoacrylate) injection
    - IGV, GOV2
      - Gluing; ↓ bleeding (vs NSBB or observation), ↓ mortality (vs observation)
    - TIPS
    - BRT0

- Primary prevention (prevention of first VH)
    - GOV1 as per EV
    - IGV1, GOV2 NSBB
    - Do not use TIPS. BRT0

Abbreviations: BRT0, balloon occluded retrograde transvenous obliteration; TIPS, transjugular intrahepatic portosystemic shunt

- ❖ Treatment of acute bleeding from gastric varices
  - Volume resuscitation
    - Restricted PRBC transfer to hemoglobin 70-90 g/dL
  - Vasoactive drugs
  - Antibiotics
  - Proton pump inhibitors
  - EGD for GOV1, IGV2
    - Esophageal variceal ligation (EVL) vs glue injection ↑ rebleeding
    - Must be performed by expert (catastrophic bleeding)
  - Balloon tamponate
    - Inflate only the gastric balloon of tubes
      - Sengstaken-Blakemore
      - Minesota
      - Linton-Nachlas
  - TIPS
    - Failure of EVL / glue
    - Cardiofundal varices

#### Acute bleeding from gastric varices (GV)

- IV infusion, restrictive transfusion of PRBC, antibiotics, vasoactive agents, plus intestinal therapy depending upon type of GV.
    - GOV1
      - EVL or injection of cyanoacrylate glue
    - IGV1/GOV2 (gastrofundal varices)
      - TIPS



## SO YOU WANT TO BE A GASTROENTEROLOGIST!

- Both EVL and EGD with glue injection into GV are effective for initial control of bleeding of gastric varices.
- Give why EBL of GV must be done by an expert endoscopist.
  - Catastrophic rebleeding will occur unless
    - Only small GV are banded
    - Both the mucosal and contralateral wall of the EV must be ligated
  - Failure to section and band both the mucosal and the contralateral wall of the GV will leave an ulcer over the vessel when the band falls off → catastrophic bleeding

### ➤ Prevention of rebleeding of GV

| Recovery from Acute GV Bleed                      | Prevention of Rebleeding GV             |
|---------------------------------------------------|-----------------------------------------|
| ○ GOV1                                            | - NSBB plus EVL, or<br>- Glue injection |
| ○ IGV1, GOV2`                                     | - TIPS, or<br>- BRTO                    |
| ○ When TIPS / BRTO not technically glue injection |                                         |

### Balloon Occluded Retrograde Transverse Obstruction (BRTO)

- Cannulate jugular or femoral vein → retrograde cannulation left renal vein → balloon occlusion and sclerosis of enlarged gastro- / splenorenal venous collaterals
- Give the pros and cons of TIPS vs BRTO in treating varices from cirrhotic portal hypertension.

|                                               | BRTO |
|-----------------------------------------------|------|
| ○ Maintain portal venous inflow to liver TIPS | +    |
| ○ Does not ↑ portal pressure                  | +    |

### ❖ Refractory ascites, previous spontaneous bacterial peritonitis (SBP)

For primary or secondary prophylaxis of EGVB, limit NSBBs to no more than the maximum recommended dose for persons with ascites (1/2 maximum recommended dose for persons with no ascites).

|               | Maximum Daily Doses, mg/day               |         |
|---------------|-------------------------------------------|---------|
|               | No Ascites                                | Ascites |
| ○ Propranolol | 320                                       | 160     |
| ○ Nadolol     | 160                                       | 80      |
| ○ Carvedilol  | Not recommended for secondary prophylaxis |         |



## ECTOPIC VARICES

### ➤ Common sites

- Small intestine
- Colon
- Sites of surgical stomas

### Treatment

- Multidisciplinary approach using large menu of options
  - EVL
    - Cyanoacrylate
      - Injection
      - Sclerosants
      - Coils
  - TIPS +/- embolization
  - BRTO
- Suggested additional reading
  - Gascia-Pafan JC, et al. Use of early TIPS for high-risk variceal bleeding. J Hepatol 2013; 58: 45-50
  - Bhat YM, et al. Tissue adhesives: Cyanoacrylate glue and fibrin sealant. Gastrointestinal Endosc 2013; 78: 209-215

“Success is liking yourself, liking what you do, and  
liking how you do it.”

Maya Angelou



## FOCAL LIVER LESIONS (FLL): AGA GUIDELINES

Abbreviations: AGA, American Gastroenterology Association

Marrero JA, et al. Am J Gastroenterol. 2014;109(9):1328-47.

- Acute / chronic liver disease
  - Abdominal ultrasound
  - Cirrhosis plus focal liver lesion (FLL) > 1 cm
    - ↓
    - CT / MRI dynamic contrast-enhanced
      - ↓
      - ↑ arterial phase, delayed venous wash-out phase
        - Negative
          - ↙
          - Liver biopsy (adenoma)
        - Positive
          - ↘
          - HCC
  - Avoid
    - Oral contraceptive agents, hormone-containing IUD,
    - Pregnancy if adenoma ≥ 5 cm
      - ↓ ≥ 5 cm
      - Tumour embolization / surgical resection

“Success is not how high you have climbed, but  
how you make a positive difference to the world.”

Roy T. Bennett, The Light in the Heart



## HEPATOCELLULAR CANCER (HCC)

### ➤ Demography

- HCC accounts for 7% of all cancers, and represents the 6<sup>th</sup> most common cancer worldwide
- About 1/3 of cirrhotics will develop HCC worldwide
- Give the three most common cancers, and the 3 most common cancers causing cancer death.

|                                            | Top 3 Cancers                                                                                    | Top 3 Cancer Deaths                                                                          |
|--------------------------------------------|--------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------|
| ○ M / F 2.4 to 1                           | <ul style="list-style-type: none"> <li>- Lung</li> <li>- Breast</li> <li>- Colorectum</li> </ul> | <ul style="list-style-type: none"> <li>▪ Lung</li> <li>▪ Stomach</li> <li>▪ Liver</li> </ul> |
| ○ Annual rates of HCC in cirrhotics due to |                                                                                                  |                                                                                              |
| - HBV 2%                                   |                                                                                                  |                                                                                              |
| - HCV 4%                                   |                                                                                                  |                                                                                              |
| - Overall 1 – 8%                           |                                                                                                  |                                                                                              |

### ➤ Pathology / histopathology

- Give the pathological subclasses of very early HCC, BCLC stage 0.
  - Vaguely nodular
  - Nodular
- Give the major differences between the vaguely nodular (VNOD) and nodular (NOD) very early HCC.

| Characteristics                                                      | VNOD  | NOD                                         |
|----------------------------------------------------------------------|-------|---------------------------------------------|
| ○ Mean size                                                          | 12 mm | 16 mm                                       |
| ○ Local invasiveness                                                 | No    | Yes (metastases)<br>Local 10%<br>Portal 25% |
| ○ Well-differentiated                                                | Yes   | No                                          |
| ○ BCLC Stage A (early HCC)<br>1 HCC > 2-5 cm, or<br>3 HCC < 3 cm     |       |                                             |
| - Size #                                                             |       |                                             |
| - Vascular invasion                                                  |       |                                             |
| ▪ No                                                                 |       |                                             |
| - Liver function                                                     |       |                                             |
| ▪ Child-Pugh A or B                                                  |       |                                             |
| ▪ No portal hypertension, bilirubin normal                           |       |                                             |
| - ECOG (good health status)                                          |       |                                             |
| - 5 yr survival 50 -70% (resection, transplantation, local ablation) |       |                                             |



- BCLC stage B (intermediate HCC)
  - Size / # nodules
  - Vascular invasion                      No
  - Liver function
- ECOG
  - Asymptomatic
  - 2 yr survival ~ 50% (chemoembolization)
- BCLC C (advanced HCC)
  - Size / # nodules
  - Vascular invasion + segmental, or portal, nodes, metastases
  - Liver function
  - ECOG symptoms
  - Survival 1 – 2 yr survival 25%
- BCLC D (end stage HCC)

Performance status ECOG 3 – 4  
1 yr survival ~ 10%

| Features                      | BCLC                       |              |     |      |
|-------------------------------|----------------------------|--------------|-----|------|
|                               | A                          | B            | C   | D    |
| ○ Size / #                    | 1 > 2-5 mm, or<br>3 < 3 cm | Multinodular |     |      |
| ○ Vascular invasion           | -                          | -            | +   |      |
| ○ Liver function (child-Pugh) | A, B                       |              |     |      |
| ○ ECOG                        | 0                          | 0            | 1-2 | 3-4  |
| ○ Survival rate               | 50-70%                     | ~50%         | 25% | ~10% |

➤ Causes / associations

- HBV
  - HBeAg positive
  - Genotype C
  - ↑ viral load
- HCV
  - Genotype 1b
- HIV plus HBV / HCV, plus
- Obesity, diabetes, fatty liver
- Smokers





- Factors associated with ↓ HCC risk
  - Vaccination against HBV
  - Treatment of HBV / HCV (possible)
    - Sustained virological response
  - Surveillance ultrasonography

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- Give the names of the fungi which contaminate food staples in parts of Asia and Africa which increase the risk of HCC, especially in persons with HBV infection and TP53 mutations.
  - *Aspergillus flavus*
  - *Aspergillus parasiticus*
- Diagnostic imaging
  - Abdominal ultrasound (US)
    - Mass echogeneity ↑, N plus halo, mixed
    - Performance characteristics (for HCC screening)
      - Depend in size of masses
      - Presence of nodular cirrhosis
      - Overall
        - Sensitivity 65-80%
        - Specificity > 90%
        - False positive rate 2.9%
      - Surveillance interval q 6 mon (even in persons at ↑ risk of HCC)
      - For masses 1-2 cm (contrast enhanced US plus MRI)
        - PPV 100%
        - NPV 42%, > 1 cm
      - Many masses < 1 cm in the cirrhotic liver are not HCC, so US of a < 1 cm
  - CT / MRI contrasted mass must be repeated q 3 mon (smaller masses are less likely to have microscopic vascular invasion)
    - Note: contrast enhanced US is less specific
  - Because of the neo-oncogenic activity of HCC progression, the blood supply becomes increasingly from the hepatic artery, rather than the usual major supply from the portal vein.
  - A mass seen in the liver of a patient with cirrhosis or high-risk non-cirrhotic conditions must then have a 4-phase multidetector CT scan (MDCT; HCC protocol)
    - The finding of both ↑ arterial phase plus venous / delayed wash out is sufficient for the diagnosis of HCC
      - 4 phases are unenhanced, arterial, venous, delayed.
    - If 4-phase MDCT is indeterminant or negative in a patient at risk, use MRI with contrast to examine for the same features (↑ arterial phase plus venous / delayed phase washout)

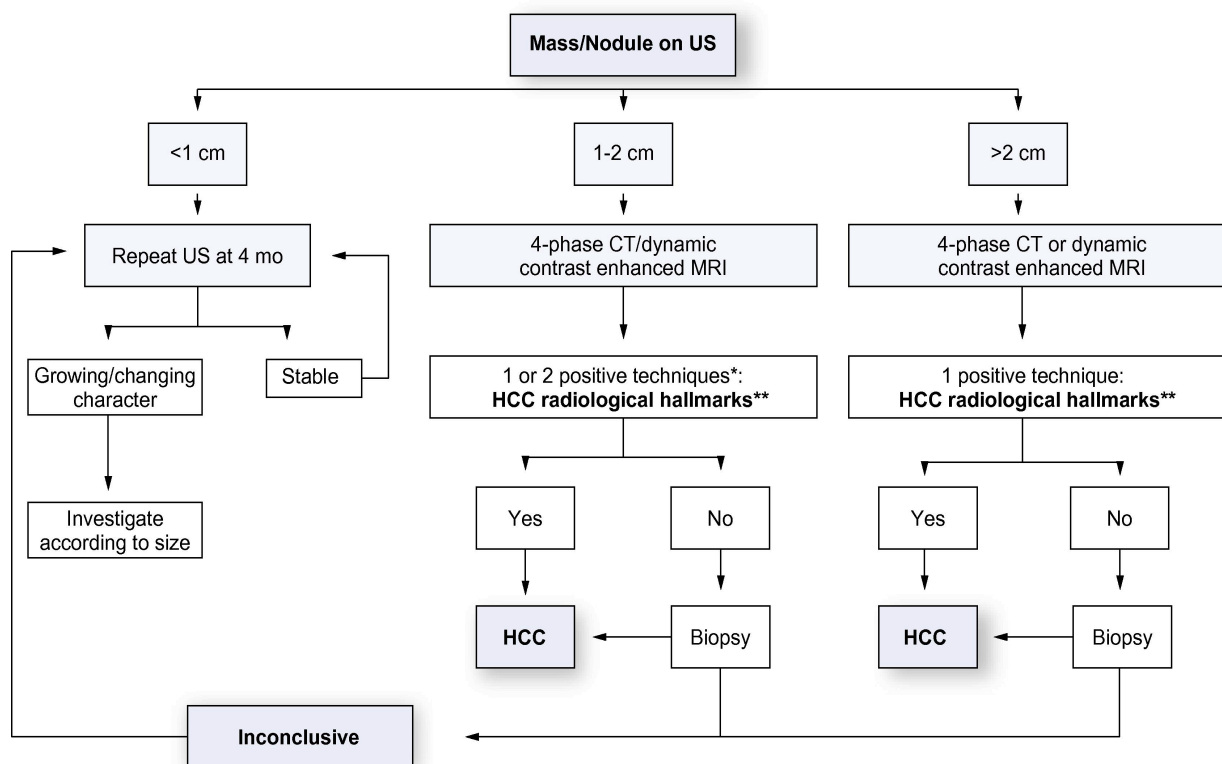
Abbreviation: BCLC, Barcelona-Clinic Liver Cancer Staging System



## Diagnostic Algorithm for Suspected HCC: AASLD / EASL and EORTC Guidelines

Abbreviations: AASLD, American Association for the Study of Liver Diseases; EASL, European Association for the Study of Liver; EORTC, European Organization for Research and Treatment of Cancer

AASLD – Bruix J and Sherman M. Hepatology 2011; 53: 1020-1022; and Heimback JK, et al. Hepatology;67(1):358-380; EASL – EORTC J. Hepatol 2012; 56: 908-943.



\*One imaging technique only recommended in centers of excellence with high-end radiological equipment. \*\*HCC radiological hallmark: arterial hypervascularity and venous / late phase washout.

Printed with permission: EASL – EORTC J. Hepatol 2012; 56: 908-943.

### Diagnostic Dilemma

- Abdominal ultrasound (US) with contrast is not first choice for HCC diagnosis, since US microbubbles are in the vascular space
- With contrast-enhanced CT, the iodination is in the extravascular space to detect HCC
- Likewise, with gadolinium-based MR imaging, the contrast passes into the extracellular space, rather than staying in the intravascular space



### Small Print Details

- The contrast enhanced CT/MRI show features compatible with the diagnosis of HCC, give the subtypes of HCC which do not have ↑ arterial phase plus ↑ venous /delayed washout phase.
  - Hypovascular HCC
    - < 2 cm, lesion still has some portal blood supply
      - ↓
      - Enlargement → just arterial supply, with typical CT/MRI features of HCC
      - Very large HCC may be hypovascular
  - High grade dysplastic nodules, (HGDN)
    - Liver biopsy may be necessary to show stromal invasion in HCC but not in HGDN
      - Note: invasion of the portal space does not distinguish between HCC and HGDN

### Diagnostic Caution

- Even the most sensitive diagnostic imaging underestimates HCC extent by ~ 25%

### ➤ Staging

- BCLC (Barcelona-Clinic Liver Cancer) Staging system
  - HCC
    - Size
    - Number Vascular invasion, N1, M1
  - Child-Pugh stage A to D
  - PST (physical standard test; physical status and cancer related symptoms) 0-2
- BCLC stage 0 (very early HCC)
  - Size / #
    - 1 HCC < 2 cm (diameter)
    - Vascular invasion / satellites
  - Liver function
    - Child-Pugh A class
  - Good health status
  - 5 yr survival 80-90% (liver resection, or transplantation)

### ➤ Screening and surveillance

- Screening and surveillance for HCC is considered to be appropriate if the underlying liver condition has an incidence of HCC  $\geq 1.5\%$  per yr of surveillance
- This incidence of 1.5 / yr includes persons with cirrhosis, as well as precirrhotic conditions:
  - HBV health carriers
    - African race > 20
    - Asian-males > 30
    - Females > 40



## ❖ Surveillance EASL – EORTC

- Cirrhosis
  - CP stage
    - A and B
    - C, awaiting liver transplantation
- Non-cirrhotic
  - HBV carrier
    - Active hepatitis, or
    - Family history of HCC
  - HCV
    - Chronic hepatitis and
    - Liver fibrosis F3
    - The 5-yr risk of non-cirrhotic HCC is 4.8% at 5 yr, slightly below the orbital figure of 1.5%
    - The risk factor of HCC in non-cirrhotic HCC are
      - Older
      - African race – esophageal varices
      - ↓ platelets ( $< 100 \times 10^9/L$ )
      - ↑ alkaline phosphatase
- Other studies suggest additional risk factors for HCC in HCV

## Practice Alert

- HCC may occur in non-cirrhotic HCV (Metavir F3 bridging fibrosis in the absence of cirrhosis).
- Stay tuned; the role of transient elastography in screening for HCC in HCV is not yet known
  - ↑ AFP (alpha fetoprotein)
  - ↑ viral load
  - Histopathology
    - Macro-regenerative modules
    - Irregular margin of nodules
    - Dysplasia
    - ↑ labeling index
      - Nuclear antigen
      - Nucleolar organization

## ❖ Intraoperative ultrasound

## Prediction of 5-yr survival rates

|                      | Size   |        |        | Number |                    |
|----------------------|--------|--------|--------|--------|--------------------|
| ○ 5 yr survival rate | ≤ 2 cm | 2-5 cm | > 5 cm | 1      | ≥ 2 (multinodular) |
|                      | 66%    | 52%    | 37%    | 57%    | 26%                |

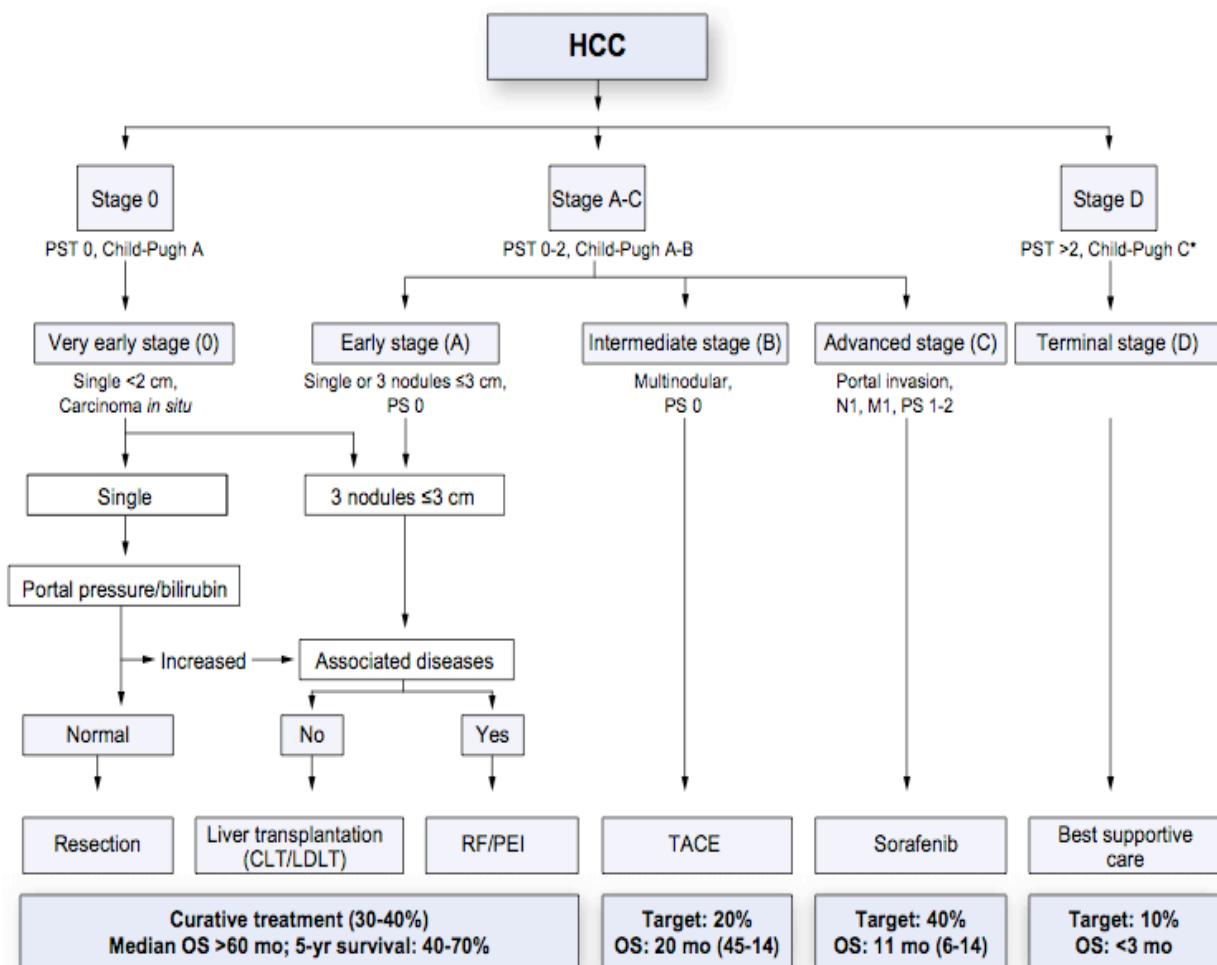


- Give the immunostains which may help in the diagnosis of HCC when the histological pattern is atypical.
  - Major markers
    - GPC3
    - HSP70
    - Glutamine synthetase
  - Gene expression profiles
    - GPC3
    - LYVE1
    - Survivin
  - Progenitor features
    - K19
    - EpCAM
  - Neovascularization
    - CD34

➤ Treatment

BCLC Staging System and Treatment Strategy: EASL–EORTC Guidelines

Abbreviation: BCLC, Barcelona Clinic Liver Cancer Group; EASL, European Association for the Study of the Liver; EORTC, European Organization for Research and Treatment of Cancer

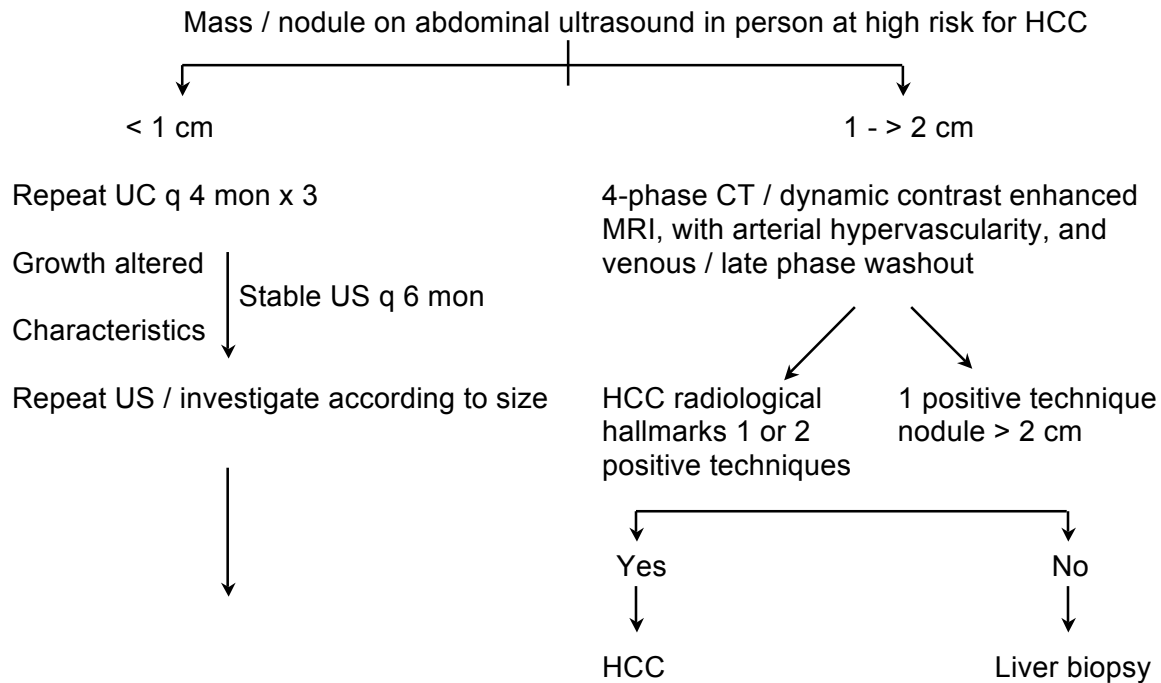


Printed with permission: EASL–EORTC Clinical Practice Guidelines: Management of hepatocellular carcinoma. J Hepatology 2012, 56: 908-943.



- Persons at high risk for HCC
  - ❖ EASL – EORTC criteria
    - Cirrhosis Child-Pugh
      - A, B
      - C, awaiting liver transplantation
    - No cirrhosis
      - HBV carriers
        - Active hepatitis
        - Family history of HCC
  - ❖ AASLD criteria
    - Chronic HCV plus fibrosis F<sup>3</sup>
      - African Canadians > 20
      - Asian Canadians
        - F > 40
        - M > 50
      - Possibly other high risk non-cirrhotic causes of HCC
        - Hereditary hemochromatosis
        - $\alpha$ 1-antitrypsin deficiency
        - NAFLD / NASH
    - Note:
      - Post-treatment
        - HBV
          - HBeAg seroconversion
          - Sustained HBV-DNA suppression
        - HCV
          - Sustained virological response and advanced fibrosis
- ↓
- Abdominal ultrasound
  - ❖ EASL – EORTC
    - Cirrhosis nodules
      - < 1 cm
    - q 4 mon x 3, then q 6 mon
    - 1-2 cm
      - Diagnostic imaging: 4-phase multidetector CT scan or dynamic contrast-enhanced MRI (HCC radiological hallmark arterial hypervascularity and venous / late phase washout)
      - Liver biopsy: Criteria of International Consensus Panel (AASLD of biopsy negative for HCC continue US q 3-6 mon)
      - Differentiate nodules with HGD from HCC with immunostaining (GPC3, HSP70, glutamine synthetase)
      - Gene expression profiles (GPC3, LYVE1, survivin)
  - ❖ AASLD
    - The surveillance interval does not need to be shortened for patients at high risk of HCC





- BCLC staging system (O to D)
  - Liver
    - Tumour size, number, vascular invasion, N1, M1
    - Function Child-Pugh's albumin, bilirubin, ascites, PHT
  - Patient
    - Performance characteristics
    - ECOG health status classification and symptoms

#### ❖ A: Liver resection

- Indications
  - HCC
  - Good liver function
    - Bilirubin normal
    - Platelets  $\geq 100,000$
    - HVPg  $\leq 10$  mmHg
- Outcomes
  - Perioperative mortality 2-3%
  - HCC recurrence 70% in 5 yr



#### ❖ B: Liver transplantation (CLT or LDLT)

- Indications
    - Milan criteria
      - 1 tumour  $< 5$  cm, or
      - $\leq 3$  tumours  $\leq 3$  cm
    - Neoadjuvant therapy
- Patients / tumours not suitable for LT



- Outcomes
  - Perioperative mortality 3%
  - One year mortality < 10%



❖ C: Local ablation

- Indications
  - BCLC O-A tumours, not suitable for surgery
  - RFA for HCC < 5 cm (response more predictable than for PEI)
- Outcomes
  - Complete response in 90% for BCLC O and HCC < 2 cm



❖ D: TACE

- Indications
  - BCLC B
  - Multinodular asymptomatic tumours with no
    - Vascular invasion
    - Extrahepatic spread

Abbreviations: AE, adverse effects; CLT, cadaveric liver transplantation; HGD, high grade dysplasia; HVPG, hepatic venous pressure gradient; LDLT, living transplantation; M, metastasis classification; N, node classification; OLT, orthotopic liver transplantation; PEI, percutaneous ethanol injection; PS, performance status; RF, radiofrequency ablation; TACE, transarterial chemoembolization

❖ Systemic therapy (sorafenib)

- Indications
  - Child-Pugh
  - BCLC C stage, or
  - HCC beyond locoregional therapies

❖ Palliative

- Pain
  - Analgesia
  - Radiotherapy for bone metastases
- Nutrition
- Psychological, social and spiritual support

❖ Hepatic Resection

- Peri-operative mortality rates
  - Hepatic resection 2-3%
  - Liver transplantation 3-10%





- Give the features which are used to predict the absence of clinical significant portal hypertension (PHT) in a cirrhotic patient with HCC being considered for a hepatic resection.
  - Varices – No
  - Ascites – Diuretics needed for treatment
  - Bilirubin concentration – Normal
  - Platelets  $< 10^5/\text{mm}^3$  (associated with splenomegaly)
  - Hepatic vein wedge pressure (HVWP) gradient  $< 10 \text{ mm Hg}$

The risk of HCC after resection is  $> 70\%$  at 5 yr. Most of these are due not to metachronous lesions but instead as a result of microvascular invasion from the original HCC tumour.

- Give the treatment of recurrent HCC after hepatic resection.

1 tumour      Repeat resection

$\geq 2$  tumours      Salvage liver transplantation (LT)

#### ❖ Liver transplantation

Milan criteria      1,  $< 5 \text{ cm}$ , or  
                                           $\leq 3$ ,  $> 3 \text{ cm}$

5 yr survival  $> 70\%$  (50% for “extended” criteria)

#### Memory Moment

- In a cirrhotic patient with a mass  $< 1 \text{ cm}$ , repeat abdominal ultrasound of the liver q 3 mon x 4, then q 6 mon (EASL – EORTC)

#### Downstaging of Upstaging

- The UCSF represents expanded /extended criteria for liver transplantation.
- EASL – EORTC recommendation: “...it is recommended not to allow the extension of the criteria for transplant eligibility, except in the context of research periods

#### LT Watch

- If the waiting period for liver transplantation is  $> 12 \text{ mon}$ , then 25% of HCC patients who were previously within the Milan criteria will have had sufficient further growth of their HCC to be dropped from the liver transplantation list.

#### Note:

- The MELD score does **not** predict the rate of drop-out of patients listed for liver transplantation for the indication of HCC.



- Living donor liver transplantation (LDLT) for HCC
  - Consider right hepatic lobe LDLT “ .... If the waiting time (for cadaveric liver donation) is expected to be so long that there is a high risk of tumour progression leading to exclusion from the waiting list” (Bruix and Sherman. Hepatology. Recommendation 13, page 20)
- MELD score exceptions
  - Additional points given for
    - HCC
      - MELD 22 if 1, 2-5 cm
      - 3, each < 3 cm
      - 10% point increase for q 3 mon on waiting list
    - Na<sub>s</sub><sup>+</sup> (hyponatremia)

Note: TACE or ablation may be applied in selected patients to “downsize” the tumour burden to fit within the Milan criteria, especially if the waiting time for LT > 6 mon.

- Prevention of reinfection in transplanted liver
  - HBV
  - HCV
- Go online for most recent date

#### ❖ Percutaneous Local Ablation Therapy

- Perform under ultrasound guidance.
  - Injection
    - Alcohol\*
  - Temperature
    - Radiofrequency\*
    - Cryotherapy
    - Laser
    - Microwave

\* first choice

#### Success of local ablation

|                                 | HCC size                                                                                                                                                                                                                                                                                      | % necrosis of HCC                                            |
|---------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------|
| ○ Ethanol                       | < 2 cm                                                                                                                                                                                                                                                                                        | 90-100%                                                      |
|                                 | 2-3 cm                                                                                                                                                                                                                                                                                        | 70%                                                          |
|                                 | 3-5 cm                                                                                                                                                                                                                                                                                        | 50%                                                          |
| -                               | May require repeated injections of ethanol to achieve complete necrosis of HCC, especially if tumour > 3 cm                                                                                                                                                                                   |                                                              |
| ○ Radiofrequency ablation (RFA) | Compared to ethanol                                                                                                                                                                                                                                                                           | < 2 cm RFA = Ethanol (RFA required fewer treatment sessions) |
| ○ Follow up                     | - CT / MR q 3 mon for 2 yr, then less frequent diagnostic imaging monitoring                                                                                                                                                                                                                  |                                                              |
| ○ Note                          | - There is incomplete evidence supporting the benefit of radioembolization of microspheres coated with the B-emitting isotope which have shown an increased survival time: <ul style="list-style-type: none"> <li>▪ Intermediate disease 17 mon</li> <li>▪ Advanced disease 12 mon</li> </ul> |                                                              |
|                                 | } Survival time                                                                                                                                                                                                                                                                               |                                                              |



- ❖ Transarterial Chemoembolization (TACE) and Transcatheter Arterial Embolization (TAE)
  - Used for patients with advanced HCC which is not suitable to be treated by surgical resection, transplantation, or percutaneous ablation
    - Chemotherapeutic drugs usually used: Cisplatin, Doxorubicin
  - Because TAE / TACE can result in extensive necrosis of both tumours and normal liver tissue, these procedures should not be used in persons with HCC with limited hepatic reserve, i.e., Child-Pugh class B or C
  - A further complication of TAE / TACE is the development of the post-embolization syndrome in 50%

Treatment Alert: TACE must not be used in the presence of ascites

- TACE may be beneficial to some patients with hepatocellular carcinoma (HCC) who are not candidates for surgery (liver resection or transplantation, or ablative therapy).
- The outcome of TACE is variable, and the hepatoma arterial-embolization prognostic (HAP) score has been developed and modified (removal of hyperbilirubinemia  $\geq 17$  mmol/L) to predict survival of patients with HCC treated with TACE.
- The modified HAP score is determined from the presence of
  - Hypoalbuminemia
  - Tumour  $> 7$  cm at diagnosis
  - $\alpha$ -fetoprotein  $\geq 400$  ng/mL
- The authors proposed that “ This system [modified HAP score] might be used to identify patients with HCC [who are] most likely to benefit from TACE in clinical practice”

Pinato DJ, et al. Clin Gastro Hepatol 2015; 13: 1204-1208.

- Give the features of the post-embolization (TAE / TACE) syndrome.
  - TAE / TACE  $\rightarrow$  Arterial obstruction  $\rightarrow$  Tumour necrosis  $\rightarrow$  Abscess / cholecystitis  $\rightarrow$ 
    - Abdominal pain
    - Fever
    - Ileus

CT / MRI is performed after TAE / TACE to determine the adequacy of necrosis. Arterial obstruction results in bubbles appearing in the tumour.

- Give the cause of the bubbles in the HCC tissue seen on CT / MRI after TAE / TACE.
  - Arterial obstruction causes necrosis of the HCC tissue, with tissue liquefaction.
  - TAE / TACE incompletely destroy tumour tissue, but the rate of vascular invasion is less, so there is  $\downarrow$  tumour progression which results in  $\uparrow$  patient survival (20% - 60% at 2 yr)

#### ❖ Sorafenib

- Pharmacology
  - Multikinase inhibitor, with activity against
 

|         |          |
|---------|----------|
| ▪ B-Raf | ▪ Raf-1  |
| ▪ C-kit | ▪ VEGFR2 |
| ▪ PDGFR |          |
- Indication
  - HCC treatment when no other treatment is available for Child A
- Prolongs median survival by  $\sim 4$  mon (5.5 to 9.2 mn)
- Sorafenib therapy must be stopped in  $\sim 10\%$  of patients, mainly to diarrhea, fatigue,  $\downarrow$  weight, and hand-foot skin reaction.



## LIVER TRANSPLANTATION (LT): EASL GUIDELINES

Abbreviations: EASL, European Association for the Study of the Liver

EASL Guidelines. J Hepatology 2016;64(2):433-485.

### ➤ Indications

- ↑ MELD score ( $\sim > 17$ , depending upon Liver Transplantation Centre) is the standard, with exceptions where additional MELD points are added.
- Give the exceptions to the MELD score.
  - Complications of cirrhosis
    - Hepatocellular cancer
    - Hyponatremia ( $\text{Na}^+_s$ )
    - Recurrent
      - GI bleeding
      - Ascites
      - Hepatic encephalopathy (also chronic encephalopathy)
    - Pruritis, intractable
    - Lung
      - Portopulmonary hypertension
      - Hepatorenal syndrome
    - Hepatovenous obstruction (Budd-Chiari syndrome [BCS])
  - Biliary tree
    - Cholangiocarcinoma (and other rare tumours)
  - Inherited / metabolic disease
    - Lung
      - Cystic fibrosis
    - Kidney
      - Primary oxaluria
    - Skin
      - Hereditary hemorrhagic telangiectasia
    - PNS
      - Familial amyloidotic polyneuropathy

### Indications to liver transplantation (LT)

- LT should be considered in any patient with end-stage liver disease
  - In whom the LT would extend life expectancy beyond what the natural history of underlying liver disease would predict
  - In whom LT is likely to improve the quality of life (QoL)
- LT is indicated in patients with
  - End-stage liver disease
  - The development of hepatocellular carcinoma (HCC)
  - Acute liver failure (ALF)
- Patients should be referred to transplant centres when major complications of cirrhosis (such as variceal hemorrhage, ascites, hepatorenal syndrome and encephalopathy (HE) occur)



## Score and prognostic factors for end-stage liver disease

- The timing of LT is crucial since patients who should be transplanted for end-stage liver disease (ESLD) need to undergo surgery before life-threatening systemic complications occur
  - They should not be transplanted too early since the advantage of transplant might be unbalanced by the risk of surgery and immune-suppression for all life.
- The MELD score was developed to determine the short term prognosis for patients undergoing TIPS after gastrointestinal bleeding and then proposed for predicting 3-mon mortality in patients with end-stage liver disease.
- In patients with MELD < 14, 1-yr survival was lower with rather than without transplantation.
  - Consequently, a MELD score > 15 is recommended to list patients with end-stage liver disease
  - In very sick patients with MELD > 30 the risk of mortality and morbidity after transplantation should be addressed
  - MELD does not reflect the impact of certain complications such as refractory ascites and recurrent encephalopathy in the risk of mortality without transplantation
  - For this reason, there are “exceptions” given to the MELD score so as to accommodate the impact of these complications on the patient’s outcome and
    - To improve the predictive value of the MELD score

- Common conditions requiring liver transplantation

## ❖ HBV Liver Disease

- HBV DNA positive (including fulminant / severe hepatitis) → immediately begin therapy with nucleotide(s) drugs (NUCs)
  - Entecavir                      ▪ ↓ HBV recurrence post-LT
  - Tenofovir                     ▪ ↑ hepatic function
  - NUCs may ↑ hepatic function / ↓ MELD score sufficient for patient to be delisted for LT
  - Cautions: do not use
    - Interferon (IFN)
    - Lamivudine
      - ↓ potency
      - ↑ risk of resistance developing
      - Use tenofovir for lamivudine resistance
    - Resistance to adefovir
      - Use entecavir

## Treatment Tips

- Co-infection with HDV (HBV plus HDV)
  - NUCs for HBV and LT
- NUCs, especially entecavir
  - ↑ risk of lactic acidosis, when MELD  $\geq 20$
- ~ 1/4 of patient's treated with NUCs and on the transplantation list will die in the first 6 mon of treatment



### Assessment for LT: MELD Score

- Evaluation for LT should be considered when a major complication of cirrhosis occurs.
- MELD score is good to predict short term pretransplant mortality risk and can be used in organ allocation.
  - Patients with liver diseases requiring LT, whose severity is not described by the MELD, should be recognized (such as HCC) and a different priority needs to be given to these patients by experts.

### Nucleot(s)ide

- NUCs with high genetic barrier (entecavir and tenofovir) are the first choice treatment for HBV decompensated cirrhosis as they can achieve undetectable HBV DNA and improve hepatic function, maybe avoiding LT.
- Severe HBV reactivation requires a prompt treatment with NUCs.
- As there is no predictive factors for the evolution towards liver failure, patients should be rapidly evaluated for LT despite antiviral treatment.
- Viral replication, HCC, hepatitis B immunoglobulin monophylaxis (vs. combined prophylaxis) are risk factors for HBV recurrence post-transplantation.
- Patients with fulminant or severe hepatitis may benefit from Entecavir or tenofovir.
- In patients with liver function deterioration in spite of anti-HBV therapy, active HDV infection should be ruled out. HDV replication is not a contraindication for LT.

### Exceptions to MELD Score

- Complications of cirrhosis
  - Refractory ascites
  - Recurrent gastrointestinal bleeding
  - Recurrent encephalopathy or chronic encephalopathy
  - Hepatopulmonary hypertension
  - Intractable pruritis resistance to medical therapies
- Specific liver diseases
  - Inherited
    - Familial amyloidotic polyneuropathy
    - Cystic fibrosis
    - Hereditary hemorrhagic telangiectasia
    - Polycystic liver disease
    - Primary oxaluria
  - Infection
    - Recurrent cholangitis
  - Vascular
    - Budd-Chiari syndrome
  - Uncommon metabolic disease



- Malignancy
  - Cholangiocarcinoma
  - Hepatocellular carcinoma
  - Uncommon liver tumours
- Others
  - MELD-sodium
  - Age (integrated MELD) score
  - Delta MELD (DMELD)
- Evaluation for LT should be considered when a major complication of cirrhosis occurs (Grade II-2)
- MELD score is good to predict short term pre-transplant mortality risk (Grade II-1)
- MELD is based on objective laboratory tests, and is used in organ allocation (Grade II-1)
- As the MELD has several limitations, patients with liver diseases requiring LT, whose severity is not described by the MELD, should be recognized. A different priority needs to be given to these patients by experts (Grade II-3 / III)
- HCC is a particular MELD exception that requires extra points to get access to the transplant.
- These points have to be standardized in each country and have to take into account size, number of nodules, AFP levels, recurrence after downstaging therapy (Grade II-1)

### **Management of Patients with Liver Cirrhosis (without HCC)**

- Eliminate contraindication of
  - Surgery
  - Contraindications to taking long-term immunosuppressive treatment
- Evaluating and selecting a good recipient for LT
  - Requires the collaboration of several specialists, who account for all comorbidities
- The final decision should be made within each expert centre
  - Among a multidisciplinary group of staff including transplant hepatologist, transplant surgeon, anesthetist, intensivist, cardiologist, etc., that considers the benefit and risk for each recipient.

### **Hepatitis B Virus (HBV)-related Liver Disease**

- Determine HBV status of the patient
  - In particular, the existence of HBV replication
  - Viral replication, HCC, hepatitis B immunoglobulin monophylaxis (vs combined prophylaxis) are risk factor for HBV recurrence post-transplantation (Grade II-2 / 3)
- If HBV DNA detectable → start anti-viral treatment with entecavir or tenofovir as soon as possible
- Entecavir and tenofovir (first choice) HBV decompensated cirrhosis
  - Can achieve undetectable HBV DNA improve hepatic function (may be avoiding LT) (Grade II-2)
- Severe HBV reactivation requires a prompt treatment with NUCs (Grade I)



- As there is no predictive factors for the evolution towards liver failure, patients should be rapidly evaluated for LT despite antiviral treatment (Grade III)
- Patients with fulminant or severe hepatitis may benefit from NUC treatment (entecavir or tenofovir) (grade II-3)
- In patients with liver function deterioration in spite of anti-HBV therapy, active HDV infection should be ruled out.
  - HDV replication is not a contraindication for LT (Grade II-1 / 2)

#### ❖ **HCV Liver Disease**

- Immediately begin IFN-free therapy before (while on waiting list) and after LT
  - Do not use interferon (IFN) in advanced / decompensated liver disease
  - Do not IFN plus ribavirin, boceprevir, ortelapevir
  - ↑ hepatic function in failing liver
  - ↓ HCV recurrence in grafted liver
    - CPT B / C
    - MELD > B
  - ↑ risk of bacterial infections
  - Severe adverse effects (SAEs)
- IFN-free therapy
  - Prevents HCV infection recurring in graft used in compensated / decompensated cirrhosis
- IFN-based therapy PegIFN, RBV and
  - Simeprevir (if patient is HCV genotype 1 or 4)
  - Sofosbuvir (inhibition of NSSB)
  - Daclatasin (inhibition of NSSB)

#### **Hepatitis C Virus (HCV)-related Liver Disease**

- To reduce risk of HCV recurrence LT candidates should be treated before transplant (Grade I)
- The achievement of negative HCV viral load can improve liver function either before (Grade II) or after transplant (Grade III)
- New IFN-free antiviral therapies are better tolerated and are a promising option for decompensated cirrhosis (Grade I)
  - Sofobuvir, ledipasvir and daclatavir can be used in patients with decompensated liver disease (simeprevir in patients with Child-Pugh B) (Grade II)
- Patients that could not be treated before LT need to be treated afterwards (Grade III)

#### ❖ **Alcoholic Liver Disease (ALD)**

- Alcoholic abstinence for 6 mon required before liver transplant (LT)
  - Controversial point
- Rate recidivism (risk of recurrence of alcohol consumption) depends upon duration of
  - Post LT follow-up most ALD patients who begin drinking alcohol post LT do so in mild amounts
  - Abstinence before LT
- Strong psychosocial support is needed before / after LT





- In selected patients with first episode acute alcoholic hepatitis (AAH) without the requiring 6 mon interval have been shown to do better than without LT, but this needs to be confirmed before application.

- A period of 6 months abstinence from alcohol before the transplant could improve liver function avoiding LT and could also improve compliance.
- A psychiatric and psycho-sociological evaluation and support pre- and post-LT is required for patients
- LT can be offered to highly selected patients with acute alcoholic hepatitis non-responsive to steroids therapy.

- LT for alcoholic cirrhosis has a favourable outcome, similar to other causes of end-stage liver disease
  - Develop an evaluation process based on medical and psychiatric criteria to better determine patients that would most benefit from the procedure

#### ❖ **Non-Alcoholic Fatty Liver Disease (NAFLD) and Non-alcoholic Steatohepatitis (NASH)**

- NAFLD / NASH causing decompensated cirrhosis has become the most frequent indication for LT
- Comorbidities must be carefully managed before / after LT

#### NASH

- Comorbidities such as obesity, hypertension, diabetes and dyslipidaemia need to be assessed and controlled both in the pre- and post-transplant setting as they increase morbidity (Grade III)

#### ❖ **Primary Biliary Cholangitis (PBC)**

- Patients with PBC who progress to cirrhosis despite treatment for PBC, or persons with intractable pruritis resistant to all therapies, are assessed with Mayo or MELD scores, and transplanted just as their risk of survival falls to < 1 yr.

- In PBC patients, indication for LT should be given for decompensated liver disease, complicated portal hypertension and for uncontrolled and intolerable pruritus refractory to all medical therapies (even if isolated if LT will improve the QoL) (Grade II-3)

- Ursodeoxycholic (UDCA) has improved the natural history of the disease, improve survival and the number of candidates of LT.



### ❖ **Primary Sclerosing Cholangitis (PSC)**

- Recall that PSC has indications for LT in addition to advanced cirrhosis due to the PSC, or to secondary cirrhosis
  - Recurrent cholangitis despite antibiotics
  - Cholangiocarcinoma (as well as gallbladder cancer, and HCC)
- A thorough search must be made pre-LT for cholangiocarcinoma, because about 15% of patients with PSC given a LT have CGA on careful examination of the explanted liver, and the survival of the patient's low in the situation
- In the 80% of patients with PSC who have associated ulcerative colitis (UC), attempts to bring the UC under control before the LT for the PSC

- In PSC patients, indication to LT should be given for decompensated liver disease, complicated portal hypertension and repeated episodes of cholangitis
- PSC is a risk factor for cholangiocarcinoma, thus cholangiocarcinoma should be excluded by radiological and biological markers before LT (Grade III)
- Patients with PSC and ulcerative colitis should undergo colonoscopy annually before and after LT due to the higher risk of developing colon cancer (Grade II-3)

### ❖ **Autoimmune Hepatitis (AIH)**

- Despite the use of corticosteroids / immunosuppression, some patients with AIH may develop hepatic decompensation
  - The Mayo AIH score may be useful to predict optimal timing of LT in AIH-cirrhosis
- AIH may present with acute liver failure, and urgent LT may be life-saving

- LT is indicated in patients with decompensated cirrhosis due to autoimmune hepatitis not responding to medical therapy and in cases of fulminant autoimmune hepatitis (Grade II-3)

### ❖ **Genetic Disorders: Non-Liver based**

- LT is indicated in both genetic diseases with parenchymal liver damage, and liver-based genetic disorders with prevalent extrahepatic manifestations
- If the genetic defect affects other organs, the indication to LT is less evident and should be discussed in an expert centre

### • **Wilson disease (WD)**

- LT may be indicated in WD for acute liver failure (ALF), or for decompensated cirrhosis despite treatment with copper chelators (penicillamine, tetrathiomolybdate), or blockers of intestinal absorption of copper (oral zinc).



- The indication of LT in patients with Wilson disease should be made in cases of acute liver failure or end-stage liver disease. LT can improve neurological symptoms but they can also worsen after the procedure.
  - The neurological assessment before the transplant is mandatory.

#### Therapeutic Cautions

- Suddenly stopping chelation therapy in WD may lead to ALF, for which the only treatment which is successful is LT.
- In a small proportion of patients with WD-associated CNS dysfunction, CNS symptoms may worsen with the initiation of chelation therapy, or LT.

#### • Hereditary Hemochromatosis (HH)

- Only a proportion of homozygotes for HH develop the iron-overload phenotype (low penetrance of gene)
- Goal of phlebotomy is to normalize serum ferritin concentration ( $< 50$  ng/mL), and to thereby
  - $\uparrow$  hepatic function
  - $\downarrow$  risk of cirrhosis
- Good prognosis post LT survival rates
 

|                                                                                        |   |                                                                                                              |
|----------------------------------------------------------------------------------------|---|--------------------------------------------------------------------------------------------------------------|
| <ul style="list-style-type: none"> <li>– 1 yr ~ 80%</li> <li>– ~ 5 yr ~ 75%</li> </ul> | } | <ul style="list-style-type: none"> <li>▪ Mortality due to infection 45%, cardiac dysfunction ~20%</li> </ul> |
|----------------------------------------------------------------------------------------|---|--------------------------------------------------------------------------------------------------------------|
- Alpha-1-antitrypsin deficiency

- Hereditary haemochromatosis can be an indication of LT, especially if complicated by HCC.
  - Cardiac evaluation – before LT needs to consider the cardiomyopathy associated with iron overload

#### ❖ Genetic Disorders: Liver-based (mutation in liver, but minimal hepatic parenchymal damage)

#### • Primary Hyperoxaluria type 1 (PH1)

- Autosomal recessive defect in alanine-glyoxylate aminotransferase, causing
  - $\downarrow$  conversion glyoxylate  $\rightarrow$  glycine
  - $\uparrow$  glyoxylate (calcium salts) in kidney and other tissues  $\rightarrow$  ESRD
- ~25% respond to pyridoxine
  - Others require renal transplantation (ESRD)
  - Others still require LT
- LT cures the disease by giving the patient a new liver to restore enzyme deficiency



- Timing and approach to transplant for primary hyperoxaluria type 1 are still controversial.
  - Consider combined liver-kidney or liver transplant before kidney failure

- **Familial amyloid polyneuropathy (FAP)**

- Autosomal dominant mutation in transthyretin leads to hepatic synthesis of an abnormal protein precursor of amyloid fibrosis
- These amyloid deposits
  - Affects motor, sensory and autonomic nerve function → polyneuropathy
  - Cardiomyopathy
- FAP with the Val30 Met substitution (valine to methionine at position 30) do well after early LT (5 yr survival 80%)

- Liver transplant for patient with familial amyloid polyneuropathy should be proposed as soon as symptoms appear (LT outcome is good if the patients are transplanted with no advanced disease manifestations).
  - LT is often done with the domino technique.
  - FAP liver recipients can develop polyneuropathy symptoms in a shorter time compared to FAP patients; nevertheless symptoms can be reversed by liver retransplantation.

## SO YOU WANT TO BE A GASTROENTEROLOGIST!

- In the context of LT in FAP, give the meaning of “domino transplantation”.
  - Patient with FAP has a near-normal liver function
  - Near-normal liver is transplanted into a recipient who has
    - Short life expectancy
    - ↑ risk of recurrent liver disease
  - Some LT-FAP patients will develop FAP-associated polyneuropathy, since the graft contains the mutation of TTR, and thus the amyloid deposits.
  - These FTx-FAP-polyneuropathy patients can then be transplanted again.

- ❖ **Hepatocellular Cancer (HCC)**

- The criteria for LT for HCC relate to the prediction of the risk (recurrence of HCC in the grafted liver)
- The criteria include
  - Milan
    - 1 HCC < 5 cm, or ≤ 3 HCC nodules each < 3 cm
    - Post-LT 5 yr survival 70%
  - UCSF
    - 1 HCC < 6.5 cm, or ≤ 3 nodules, the largest of which is < 4.5 cm or total diameter < 8.5 cm



- AFP model
  - Alpha-fetoprotein < 500 ng/mL, plus
  - HCC nodules size, number
  - AFP score  $\leq 2$  predicts post-LT 5-yr survival 70%

## SO YOU WANT TO BE A HEPATOLOGIST!

Pre-cirrhosis HCC is recognized in several conditions, such as HBV infection, NASH, HH. The criteria developed to predict HCC recurrence after liver transplant (LT) for the cirrhotic patient with HCC have not been validated for pre-cirrhotic HCC.

- Give the recommendations for LT for HCC in a patient with advanced liver disease but no cirrhosis.
  - Absence of
    - Short life expectancy
    - $\uparrow$  risk of recurrent liver disease
  - } Invasion
  - > 12 mon since LT performed for intrahepatic recurrence of HCC after a previous partial liver resection for HCC

- LT for HCC patients meeting Milan criteria has an excellent outcome.
  - An expansion of these criteria is acceptable if the recurrence-free survival is comparable.
  - All new models should be compared to the Milan model
- LT is usually not recommended for cholangiocarcinoma or mixed hepatocellular/cholangiocarcinoma since
  - Results are poor, but LT for perihilar cholangiocarcinoma could be offered in centres with clinical research protocols employing adjuvant or neoadjuvant therapy
- LT can be offered to patients with fibrolamellar carcinoma and epithelioid hemangioendothelioma
- Liver metastasis from non-liver tumours, such as neuroendocrine might be considered for LT in very selected patients and only in trained liver transplant centres with experience in such an indication
- Liver metastasis from colorectal cancer is usually a contraindication to LT and might be proposed in very selected patients within research trials and only in trained liver transplant centres with experience in such indication to LT

## Mangement of Patient with Liver Cirrhosis and Hepatic Malignancies

- Patients with an indication to LT should undergo extensive work-up before their inscription onto the waiting list (Grade III).
- No age limit of potential LT recipient are established, considering the good outcome of elderly patients
  - A multidisciplinary evaluation should always be performed in elderly patients to exclude comorbidities (Grade III).
- Electrocardiogram and transthoracic echocardiography should be performed in all liver transplant candidates (grade II-3).



- In patients with multiple cardiovascular risk factors and in patients older than 50 yr, a cardiopulmonary exercise test, a pharmacological stress test is the test of choice (grade II-3)
- Hepatopulmonary syndrome (HPS) is an indication to LT (Grade II-2 / 3).
- LT should be considered in patients with PPHTN responding to medical therapy with pulmonary vasodilators and with MPAP  $\leq$  35 mm Hg (Grade II-2 / 3).

#### ❖ **Cholangiocarcinoma**

- High risk of recurrence
  - Intrahepatic
  - Extrahepatic
  - Perihilar
- Neoadjuvant chemoradiation
- Surgical resection
- LT (5 yr survival rate ~2/3)

#### ❖ **Fibromellar Epithelial Hemangioendothelioma**

- Disease-free survival rates after LT
  - 1 yr, ~90%, 5 yr, ~80%; 10 yr, ~64%

#### ❖ **Colorectal Cancer Metastasis**

- Controversial; awaiting further study

#### ❖ **Neuroendocrine Tumour (NET)**

- Indications
  - Patient symptoms
  - Tumour
- Hepatomegaly
- $\uparrow\uparrow$  hormone levels  $\rightarrow$  symptoms
- Slow growing
- Diffuse metastasis
- Failed non-surgical treatment

### **Pre-Liver Transplantation Assessment for Comorbidities**

#### ❖ **Cardiovascular**

- Related to cirrhosis
  - Cirrhotic cardiomyopathy
    - $\downarrow$  contractility systolic / diastolic dysfunction
    - $\uparrow$  conduction abnormalities
- Unrelated to cirrhosis
  - Other cardiac conditions. E.g., CVD, PVD, valvular defects
- Testing
  - ECG, cardiac echocardiography
  - Cardiopulmonary exercise test (aerobic capacity, anaerobic threshold)
  - Cardiac angiography
- Encouraging
  - Once associated CAD has been effectively treated, risk of LT no different than without CAD
- Discouraging
  - Adverse effects of some post-LT medications may accelerate CAD

Abbreviations: CAD, coronary heart disease; PVD, peripheral vascular disease



- The preservation of the inferior vena cava by piggyback technique is recommended during LT whenever it is possible.
  - The use of this technique is associated with greater hemodynamic stability during surgery (Grade II-3)
- The domino transplant can be used for patients with familial amyloid polyneuropathy, as long as recipients are older than 55 years in order to reduce the risk of developing the disease (Grade II-3)
- Auxiliary transplantation may be indicated in patients with acute liver failure or functional, congenital or metabolic disorders affecting a normal liver.
  - The advantage of this type of transplantation would be the possibility of removing the graft and withdrawing the immunosuppression once the native liver returns to its normal function (Grade II-3)
- Because of the low number of available organs in paediatric LT, the use of split LT is an acceptable option, as long as the liver graft volume is sufficient.
  - In this case the child receives a graft that includes segments II and III
- Given the organ shortage, adult LDLT is recommended in the case in which there is an available donor, as long as the estimated volume of the graft is at least 0.8% of the weight of the recipient
  - In adult LT, the use of the split LT may be an alternative given the organ shortage
    - Left liver graft recipients must have a low weight.
    - Use of the left lobe of the graft is associated with worse outcomes
- It is necessary to prevent hepatic artery thrombosis during LT and post-operative period.
  - The occurrence of this complication requires retransplantation in 50% of cases
- Portal vein thrombosis prior to LT usually does not represent an absolute contraindication.
  - In cases of extensive thrombosis a non-anatomical portal revascularization technique such as a renoportal anastomosis can be performed
- If a biliary anastomosis leakage in the post-transplantation period is diagnosed, initial ERCP with sphincterotomy is recommended.
  - If the leakage persists, a temporary biliary stent can be used
- In patients with impaired coagulation, a temporary packing of 48 hours may be necessary
- In advanced cases of ischaemic cholangiopathy, the final treatment is retransplantation
- In cases of stenosis of the biliary anastomosis without improvement after conservative treatment, it is recommended to perform a hepatico-jejunostomy
- In partial grafts recipients with bile duct anastomosis stenosis or leakage, interventional radiology plays an important role (dilatation, stent insertion)
  - 50% of patients eventually require a hepatico-jejunostomy



## ❖ Pulmonary

### Work-up for Liver Transplant (LT)

- Patients with an indication to LT should undergo an extensive work-up before their inscription onto the waiting list
  - There are no age limitations for LT recipients
  - A multidisciplinary evaluation should always be performed in elderly patients to exclude comorbidities
- Testing
  - Electrocardiogram and transthoracic echocardiography should be performed in all liver transplant candidates
  - In patients with multiple cardiovascular risk factors, and in patients older than 50 years, a cardiopulmonary exercise test should be done.
  - If the target heart rate is not achieved during a standard exercise test a pharmacological stress test is the test of choice

## ❖ Hepatopulmonary Syndrome (HPS)

### ➤ Demography

- Present in ~15% of persons with cirrhosis

### ➤ Pathophysiology

- Dilation of blood vessels in basal lung

### ➤ Diagnosis

- A-aO<sub>2</sub> (alveolar-arterial O<sub>2</sub> gradient)
- Contrast echocardiography (“bubble” test)

### ➤ Clinical

- Platypnea
- Diagnosis early when
  - PaO<sub>2</sub> > 50 mm Hg
  - Reversibility to 100% O<sub>2</sub> inhalation

} Late diagnosis – may have irreversibility poor pulmonary function post-LT → ↑ mortality

### ➤ Treatment

- Early diagnosis
- When LT done for HPS
  - Pulmonary function may
    - Worsen early after LT and
    - Take months to improve
    - Thus, diagnosis and treat early





## ❖ **Portopulmonary Hypertension (PPHTN)**

- Demography
  - Present in ~5% of persons with cirrhosis
- Pathophysiology
  - Imbalance between vasoconstriction / vasodilation → neoangiogenesis → pulmonary pressure
- Diagnostic imaging
  - Echocardiogram pulmonary artery pressure (PAP) > 30 mm Hg → right heart catheterization
- Prognosis
  - Mean PPHTN  $\geq$  35 mm Hg
    - ↑ mortality post-LT
- Treatment
  - Early vasodilators
  - Pulmonary vasodilators
    - Prostacycline / prostacycline analogs
    - Endothelin receptor antagonists
    - Phosphodiesterase inhibitor type 5
  - Perioperative do not
    - ↑ preload
    - ↑ PAP

- Respiratory function needs to be assessed
  - The presence and stage of hepatopulmonary syndrome and portopulmonary hypertension should be evaluated
- Hepatopulmonary syndrome is an indication to LT
- LT should be considered in patients with PPHTN responding to medical therapy with pulmonary vasodilators and with MPAP  $\leq$  35 mmHg

## ❖ **Hepatorenal Syndrome (HRS)**

- Definition
  - Acute renal failure
    - ↑ Cr
      - Absolute 0.3 mg/dL
      - Relative to baseline 50% (1.5x)

} Occurring within 48 hr, not due to other causes (e.g., hypovolemia, acute tubular necrosis [ATN], NSAIDs, diuretics)

- Chronic renal failure
  - eGFR < 60 mL/min → modification of diet in renal disease 6 (MDRD6) formula



➤ Treatment

- Liver plus kidney transplantation
  - HRS requiring dialysis (renal replacement therapy for > 8-2 wk)
  - Renal biopsy with > 30% fibrosis / glomerulosclerosis

➤ Prognosis

- Renal failure has terrible prognosis in persons with cirrhosis 50% die within 1 mon (risk of death ↑ 7x)
  - Causes
    - Hepatorenal syndrome (HR)
    - Acute tubular necrosis
      - Hypovolemia
      - Sepsis
    - Associated renal disease

- Hepatorenal syndrome is not a contraindication to LT
- Chronic kidney disease might be severe and irreversible requiring combined liver-kidney transplant

❖ Nutrition

- No standardized protocol in cirrhotic patients
- Malnutrition, including BMI < 18.5 and > 40 → ↑ mortality
- Metabolic syndrome and its components need to be managed before / after LT

- The nutritional status is hard to assess in a cirrhotic patient.
  - The thickness and the area of psoas muscle have been correlated with worse outcome
- Improvement of nutritional status is indicated but no protocols have been approved

❖ Bone Mineral Density (BMD)

- DEXAScan for BMD must be performed pre-LT in all patients
- Smoking must be stopped, and BMI corrected

- As osteoporosis is associated with cirrhosis, densitometry should be part of liver transplant work-up



## ❖ Donor-specific Alloantibodies

- The presence of donor-specific alloantibodies has been associated with acute and chronic antibodies-mediated rejection and with several histological damages.
  - The best test and use of anti-DSA is under study

## ❖ Infection

- All LT candidates (latent infection)
- Eligible for LT
  - Serology
    - Epstein-Barr virus (EBV)
    - Human Herpes virus (HHV)
    - Varicella Zoster virus (VZV)
    - Herpes Simplex virus (HSV-1/-2)
    - Strongyloids stercoralis
    - Treponema pallidum
    - Toxoplasma gondii
    - HPV (recommended in other guidelines)
    - West Nile virus (WNV; patients in endemic areas)
    - Coccidiomycosis
  - Urine culture
  - Stool culture
  - Swab (nasal / axillary)
    - Staphylococcus aureus
- Vaccinations
  - Brought up-to-date
    - Influenza
    - HAV, HBV
    - Pneumococcus
    - Tetanus
    - Measles, mumps in the guidelines

### HIV co-infection with HBV / HCV and LT

- Treat HIV with HAART
  - Treat HBV with HAART
  - Treat HCV with interferon-free regimens

- Screening for bacterial, fungal and viral infections is mandatory before LT
- The presence of an active infection contraindicates LT
- CMV donor/recipient status determines the optimal timing of prophylaxis



### ❖ Dental Examination – Dental Infection

- Soft tissue infections / cellulitis
    - Gram-positive            *S. aureus*
    - Streptococci*
    - Gram-negative           *Klebsiella* spp
  - Treatment-related
    - Bacteremia
    - Sclerotherapy of esophageal varices
    - Transarterial chemoembolization (TACE)
  - Candidemia (particularly in PSC, with dominant stricture)
- } Treat before LT

### Extended Criteria Donors

- Calculate the donor risk index (DRI) using the Balance of Risk (BAR) score
- Risk factors for characteristics of donor which ↑ risk of post-LT graft failure
  - Patients (donor)
    - > 40 yr
    - Stroke as a cause of death
    - Previous LT
    - Caucasian
    - Dependence of life support pre-LT
    - Short stature
  - Liver
    - Cold ischemia time
    - Geographical location between donor and recipient
    - Age of recipient

### ❖ Age of Donor

- Give the negative characteristics of a liver graft being used for LT.
  - ↑ graft failure                    }    – ↑ ischemic (reperfusion injury)
  - ↑ patient mortality               }    – ↑ hepatic artery thrombosis (HAT)
  - }    – ↓ regenerative potential
- Give the additional negative characteristics of a liver graft from an old donor being given for LT in a HCV-infected recipient.
  - ↑ graft failure                    }    – Fibrosis, cholestasis
  - ↑ patient mortality               }    – Post-LT infection

- Utilisation of livers from older donors is associated with increased risk of mortality and graft loss, especially in HCV-related patients. However, in selected patients excellent results can be achieved



## ❖ HBcAb-positive donors

### ➤ Vaccination

#### Acceptable Source and Recipients

| Donor       | Recipients                      |
|-------------|---------------------------------|
| - Anti-HBc+ | HBsAg+<br>Anti-HBc+ / anti-HBs+ |
| - HBcAb+    | HBsAg+/-                        |
| - HBsAg+    | HBsAg+                          |

- Liver grafts from anti-HBc positive donors should be preferentially directed to HBV-exposed liver transplant candidates.
  - Prophylaxis of HBV recurrence in patients who received a liver from an anti-HBc positive donor should be initiated immediately after LT if recipients do not have anti-HBs. (Lamivudine monotherapy is the best cost-effective treatment)
- The use of anti-HCV positive grafts in recipients with HCV infection is generally considered safe, whereas it should be avoided in HCV negative recipients

### ➤ Prognosis

- HBcAb-positive donor liver given to HBsAg-positive recipient has better prognosis than HBcAb-positive donor liver given to HbsAg-negative recipient (anti-HBs protects from the development of de novo HBV infection)
- But HBcAb-positive donor may cause de novo HBV infection in the recipient
- Anti-HBc positive liver graft can be given to anti-HBc positive and to antiHBs positive recipients

## ❖ HCV-positive Donors

- HCV+ donor liver graft may be given to HCV+ recipient, with no adverse effect on patient-survival
  - If possible, avoid genotype I HCV+ being given to HCV+ non-genotype 1 recipient

## ❖ Diabetes Mellitus

- Diabetes in the donor may propose a risk to graft recipient, but some authorities will accept a donor liver from a diabetic to give to any recipient without HCV infection.

- Utilisation of livers from donors with diabetes mellitus might represent a good option only in HCV negative recipients



### ❖ **Steatosis**

- Avoid using liver graft with > 30% fat (by volume)
  - 5 yr survival rate for patient receiving mildly fatty liver (< 30%) ~ 60%

- Grafts with microsteatosis or mild macrosteatosis are considered suitable for transplantation.
  - Livers with moderate macrovesicular steatosis may result in acceptable outcomes in select donor-recipient combinations. Grafts with severe macrosteatosis should not be used as they are associated with increased risks of graft loss and mortality

### ❖ **Cancer Screening (age-related)**

- Lung
  - Chest X-ray, CT chest
- GI
  - Colonoscopy
  - EGD
  - Abdominal ultrasound
  - Contrast enhanced CT / MRI
  - PET scan
- GU
  - Bladder
  - Prostate
  - Cervix (pap smear)
- Breast
  - Mammography
- Skin
  - Melanoma and non-melanoma

### ❖ **Psychosocial Screening**

- Depression, anxiety
  - Psychiatric assessment
- Minimal hepatic encephalopathy (MHE)
- Social support
- Abuse
  - Alcohol, marijuana, recreational drugs, methadone-maintained opioid-dependent

- Screening for neoplastic lesions should be part of LT work-up
- The search for pulmonary neoplasia, ear-nose-throat, stomatology, oesophageal and bladder is indicated in cases of alcohol and smoking addiction
- History of a treated cancer is not an absolute contraindication to LT
  - A 5-year interval is a reasonable time between curative cancer treatment and LT (depending on type and stage of previously treated cancer)



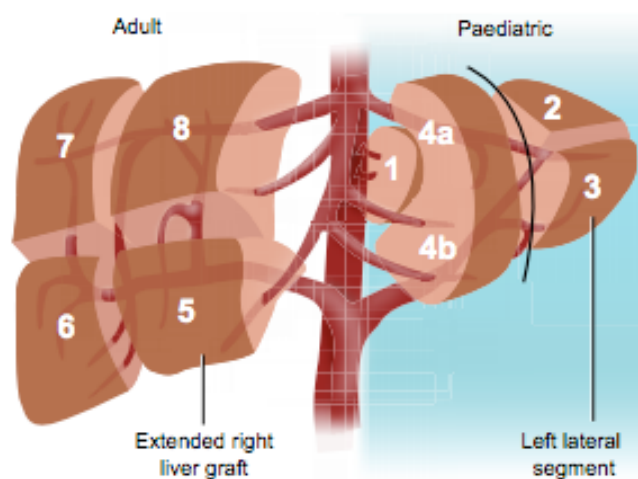
Tell this to Your Liver Transplant Patient!

- "...Smoking cessation should be mandatory in all transplant candidates"

## The Process of Liver Transplantation

- Recipient anatomical evaluation is mandatory with a three-phase intravenous contrast CT scan
- The presence of portal vein thrombosis is not a contraindication to LT
  - If the thrombosis extends to the whole porto-mesenteric system (Yerdel Stage IV), LT might not be feasible
- Assess liver size and vascular supply
  - MRI, MRCP, ERCP
- Identify and treat
  - Portocaval shunts
  - Arcuate ligament
  - Portal vein thrombosis (PVT)
    - Numerous options
    - Thrombectomy, surgical
    - Thromboendovenectomy venous graft / reconstruction
    - Portocaval hemitransposition
    - Endovascular interventions
    - Anticoagulation ↓ risk of extension of clot
- Although PVT may be treated, LT may not be possible with PVT plus thrombosis of splenic vein (SV) and superior mesenteric vein (SMV)

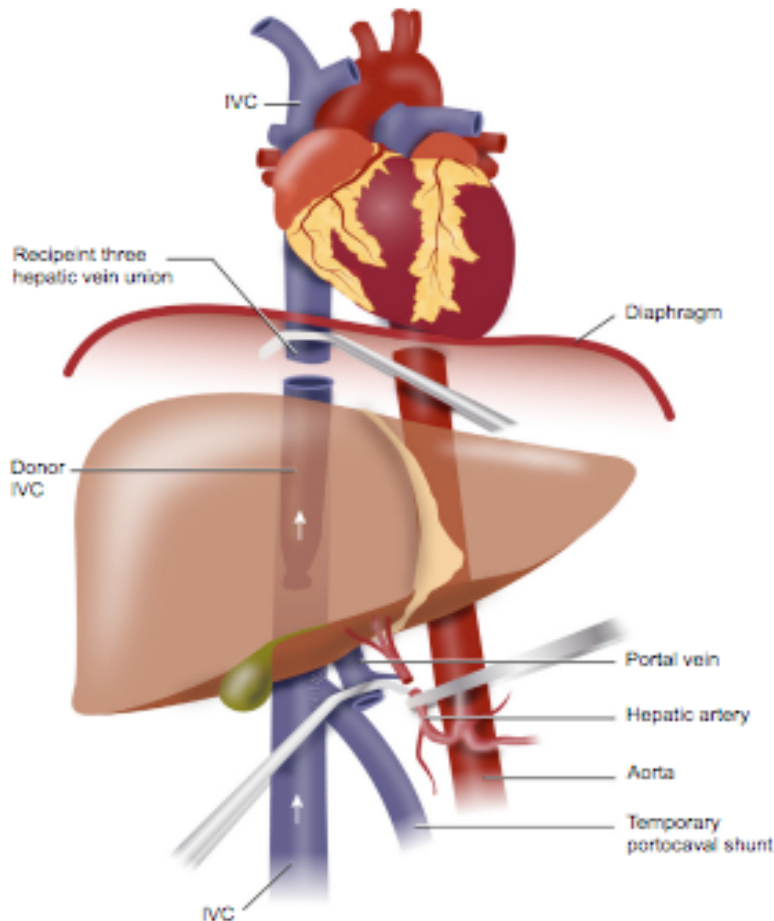
Split liver transplantation – adult and child as recipients



Printed with permission: EASL Clinical Practice Guidelines: Liver transplantation. J Hepatol. 2016;64(2):433-485, Figure 3.



Liver transplantation with piggy-back technique. Anastomosis of the recipient three hepatic vein union with the donor inferior vena cava (IVC).



Printed with permission: EASL Clinical Practice Guidelines: Liver transplantation. J Hepatol. 2016;64(2):433-485, Figure 2.

## Organ Donation

- Consent may be “opt-in” (explicit consent) or “opt-out” (presumed consent)
- Donors cadaveric
  - Donation after brain death (DBD)
  - Donation after cardiac death (DCD)
- Liver related donors (LDLT)
- Reduced / split-liver donation (pediatrics)
- Extended criteria (marginal) donors (ECD)
  - ↑ risk of ischemic type biliary lesion (TBL; aka intrahepatic biliary strictures)
    - Controlled donor cardiac death (CDCD)
    - With withdrawal of life support therapy (WLST)
    - 1- and 3-yr graft survival 80% and 70% respectively





### ❖ Previous Cancer in the Donor

- Concern
  - Transmission of donor-related malignancy
- Acceptable donors
  - CNS ▪ Low risk primary malignancy
  - Breast ▪ < T1c
  - Colon ▪ < T3
  - Skin ▪ Non-melanoma skin cancer
- Contraindicated
  - CNS ▪ Glioblastoma multiform
  - Lung ▪ Cancer
  - Skin ▪ Melanoma

#### Malignancy

- Livers from a donor with previous history of malignancy can be used in selected situations according to tumour site and its stage
- Donors with select bacterial infections can be safely used as long as appropriate therapy is provided to both the donor before procurement and the recipient after transplantation.
  - Livers from donors with isolated fungal infections should be routinely used.
  - Grafts from donors with viral or parasitic disease should be used according to the type of infection and to the severity of recipient liver disease.

### ❖ Donors with Infection

- USA CDC principle-zero tolerance for risk of transmitting infection from donor to recipient (1 zero risk)
- EASL
  - “risk cannot be entirely eliminated”
    - Stratify risk of transmitting infection to recipient, and use liver donors whose infection has a reasonably low risk of transmission
- LT contraindicated because of infection
  - Bacteria ▪ Methacillin drug resistant (MDR) bacteria
    - Vancomycin-resistant Enterococcus
    - Carbapenemase producing Klebsiella pneumonia
  - Viruses ▪ HIV – 1/2
    - Encephalitis (clinical)
    - West Nile Virus (WNV)
  - TB ▪ Active



## Post-LT Prognosis

- Overall
    - 1 yr, 90%; 5 yr, 70%
  - 5 yr survival rate ~70%
    - Condition < 70%
      - Acute liver failure (ALF) 64%
      - Malignancy HCC, 63%; metastases, 49%; cholangiocarcinoma, 31%
  - Difference in 5-versus 10-yr survival rate is about 10% lower
    - Conditions with > 10% difference between 5- and 10-yr survival
      - Alcoholic liver disease (~14%)
      - HCV infection (~12%)
      - HCC (~14%)
      - Metastases (~18%)
- Retransplantation has inferior outcome compared with the first transplant
    - Nevertheless it should be considered in cases of acute or chronic graft failure
    - A patient candidate for retransplantation should undergo a liver work-up as for the first transplant
    - HCV recurrence is not a contraindication for retransplantation

## Surgical Complications

- ❖ Vascular Arterial Complications
  - Hepatic artery thrombosis (HAT)
    - Occurs in ~5% of LT
    - HAT
      - graft dysfunction (early)
      - ischemic biliary complications (late)
    - Treatment
      - Reintervention / revascularization
      - Retransplantation
- ❖ Venous Complications
  - Inferior vena cava (IVC) anastomotic stenosis
    - Occurs in ~5% of LT
    - Hyperplasia / fibrosis → anastomotic stricture
    - Treatment
      - Endovascular techniques
    - Prevention
      - Surgical technique: “piggy-back” anastomosis of the union of the 3 hepatic veins of the recipients with the IVC of the donor graft



- Portal vein thrombosis (PHT)
  - Occurs in ~10% of LT
  - Transplantation surgeon will wish to know of presence of PVT in order to consider what is best surgical approach e.g., portocaval transposition
  - Treat with anti-coagulation (short term)

## Immunosuppression for Liver Transplantation

### ❖ Calcineurin Inhibitors (CNIs)

#### ➤ Names

- Cyclosporin (CyA)

- CNI-based immunosuppression is still the cornerstone of immunosuppressive regimens in LT. Tac results in better long-term graft and patient survival than CyA including HCV patients
  - There is no evidence that combination of MMF with CNI improves graft or patient survival compared to CNI and steroids or AZA
- Induction agents are safe when used together with CNIs, allowing a reduction of CNI dose especially in patients with pre-transplant renal impairment (Grade I)
  - Concern still remains for the high costs of IL-2R agents and their potential negative influence on tolerance

- Tacrolimus

- IL-2R antibodies with delayed and low dose Tac plus MMF and steroids is safe and improves renal function after LT
- MMF monotherapy should **not** be used due to the significantly high incidence of acute cellular rejection
- MMF in combination with CNI reduction of at least 50% is associated with significant improvement in renal function and it has a low risk of acute rejection (Grade I)
  - To date no RCTs have been performed directly comparing MMF and AZA with respect to renal function
- Conversion to SRL can be done safely and provide adequate immunosuppression without increased incidence of rejection, graft loss or infection in liver transplant recipients (Grade I)
- Early EVR-based CNI-free immunosuppression seems to improve renal function after LT
  - However, this can be responsible for an increased incidence of acute rejection

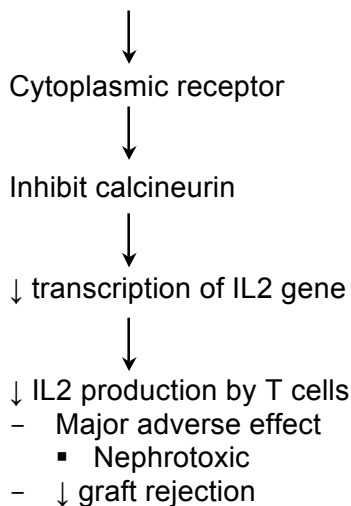


- It is not possible to conclude that there is a meaningful clinical difference between the CNIs with respect to the course of HCV recurrence after LT (Grade I)
- A rapid decrease in steroid immunosuppression could determine in some patients a worse graft evolution
- The 'protective role' of slow steroid withdrawal shown in several studies also requires further investigation
- There is still controversy regarding the best antiproliferative agent for HCV recipients.
  - Maintenance of AZA is associated with less fibrosis progression compared to MMF
- Only properly designed RCT will confirm if mTOR inhibitors are useful in HCV transplant recipients. There are very few HCV specific data on EVR (Grade III)
- OKT3 and alemtuzumab are associated with severe HCV recurrence (Grade I)
- Data for IL-2R antagonists are contradictory, most studies showing no harm, but some showing worse recurrence

- The benefit of SRL is evident in 3 - 5 years in patients with HCC within Milan criteria
  - SRL does not improve long-term recurrence-free survival beyond 5 years

➤ Mechanism of action

- CSA binds cyclophilin
- Tac binds to FK-binding protein 12



## ❖ Anti-metabolite Immunosuppressants

- Azathioprine (6-mercaptopurine)
- Mycophenolate mofetil (MMF)
- Sirolimus (SRL)
- Everolimus (EVR)

↓ Inosine monophosphate dehydrogenase (IMPDH) → ↓ synthesis of purines → ↓ proliferation of T / B cells

↓ mammalian target of rapamycin (mTOR) → ↓ IL2 / IL15 → ↓ proliferation of T / B cells

## ❖ Induction agents

- Basiliximab (CD25 / IL2 receptor) monoclonal antibodies (chimeric, humanized) → ↓ activity of activated T cells
- Polyclonal antibodies
  - Antithymocyte (ATG)
  - Antilymphocyte (ALG)

} Induction therapy with CNIs

## ❖ Retransplantation

- Occurs in 7 – 10% of LT
- Causes / associations
  - Early (< 30 d)
    - Hepatic artery thrombosis
    - Primary graft non-function
  - Late (> 30 d)
    - Ischemic biliary lesions
    - Chronic rejection
    - Recurrence of the primary liver disease (for which the LT was performed)
- ↑ mortality rate (MR)
  - Retransplantation (re-LT)
  - Mortality rate
 

|            | 1 yr | 5 yr | 10 yr |
|------------|------|------|-------|
| - No re-LT | 18%  | 28%  | 33%   |
| - Re-LT    | 39%  | 46%  | 50%   |

Early > later re-LT mortality
  - ↑ MR with re-LT associated with
    - Older donors
    - ↑ MELD score
    - > 8 hr cold ischemia time

## MCQ Trick

- Give the difference in the rate of survival for re-LT for HCV-associated liver disease.
  - It is no longer accepted that there is a survival in HCV-positive liver patients who require re-LT
    - To paraphrase
      - Mortality rate (MR) post re-LT are similar for alcoholic or cholestatic liver disease, as for cryptogenic or HCV-cirrhosis, when the MR are adjusted for age of the patient and their MELD score



### ❖ Biliary Tract Complications

- Biliary leakage
  - Occurs in ~5% of LT
  - Treatment
    - Partial graft
      - Embolization → retransplantation
    - Total graft
      - ERCP stenting
- Ischemic bile duct injuries
  - ↑ risk
    - DCD donors (occurs in ~25%)
    - ABO incompatibility
    - Ischemic / reperfusion injury
    - Recurrence of PSC (occurs in ~25%) → retransplantation

### ❖ Duct-to-Duct Anastamotic Stenosis

- Complete grafts
  - Occurs in ~5% of LT, usually in the first yr
  - Usually due to surgical technique
  - Diagnosis
    - MRCP
  - Treatment
    - ERCP with balloon dilation / stent
    - Percutaneous transhepatic cholangiography (PTC)
      - For failed endoscopic treatment or,
      - Complex hepatico-jejunostomy
- Partial grafts
  - Usually associated with
    - A bile leak
    - Large duct-to-duct anastomosis
  - Treatment
    - Interventional radiological dilation / stenting
    - Conversion / duct-to-duct anastomosis → hepatico-jejunostomy

### **Immunosuppression, LT and Special Clinical Considerations**

- Immunosuppression and renal impairment in LT recipient
  - CNIs cause reversible renal vasoconstriction and tubulointerstitial chronic fibrosis
  - IL-2R antibodies can be given to ↓ / delay of nephrotoxic effect of CNIs (CNI-sparing)
  - Everolimus (EVR) may be used in place of CNI because of its renal-sparing
- Immunosuppression and HCV infection in LT recipient
  - “a rapid reduction in the ...steroid dosage may [increase] HCV recurrence [in an HCV liver transplanted patient]”
    - Slow tapering of corticosteroids over 6 mon may be an appropriate approach
  - Do not use OKT3, alemtuzumab in HCV-infected patient
- Immunosuppression and HCC in LT recipients
  - Sirolimus (SRL) given to patient with LT for cirrhosis-associated HCC within the Milan criteria may have ↑ survival
    - Recurrence-free
    - Overall survival in first 3-5 yr



## Medical Complications

- Graft loss / death
  - 1 yr
    - Infection
    - Surgical complications
  - > 1 yr
    - Cardiovascular disease
    - Recurrence of underlying liver disease (HBV, HCV, HCC, ALD, NAFLD)
    - Malignancy, de novo
- Morbidity
  - Renal dysfunction
  - Metabolic syndrome
  - Bone disease

### Why to Treat Rejection

- Acute/chronic rejection → Chronic
- Ductopenic rejection → graft dysfunction → death

## Recurrence of Liver Disease after Liver Transplantation

### ❖ HCV Infection

- > 99% HCV recurrence of HCV infection after LT for HCV-associated cirrhosis
  - Identify “rapid fibrosis”
    - TE > 8.6 kPa
    - Biopsy F ≥ 2 METAVIR
    - HVPg ≥ 6
  - Fibrosing cholestatic hepatitis
    - Sofosbuvir +/-
    - Ledipasvir
- 1 yr after LT, predicts loss of hepatic graft
- ↓
- Anti-HCV therapy with interferon (IFN) free regimens, e.g.
    - Sofosbuvir, ledipasvir and ribavirin for 12-24 wk

- Antiviral therapy is recommended for all patients with hepatitis C recurrence
  - Treatment should be initiated early in those with significant graft damage (F ≥ 2)
  - SVR is associated with improved outcomes in these patients
  - Treatment with PegIFN and RBV has a low efficacy (SVR ~35%) and is no longer recommended in this setting
  - The addition of a first generation protein inhibitor (boceprevir, telaprevir) for genotype 1-infected patients increases efficacy but also side effects and is no longer recommended in LT recipients
- Sofosbuvir/ledipasvir plus RBV and sofosbuvir plus simeprevir (with or without RBV) are safe and achieve high SVR rates in genotype 1- and 4-infected LT recipients, including cirrhotic patients.
  - Sofosbuvir alone or in combination with ledipasvir has also shown to be safe and efficacious in severe forms of recurrence (i.e., fibrosing cholestatic hepatitis)
  - In naïve patients with mild recurrence, the combination of ABT450/r, ombitasvir, dasabuvir and RBV has shown high efficacy, but cyclosporine and Tac adjustments are necessary due to drug-drug interactions



- Follow-up of recurrent hepatitis C after LT should include a regular assessment of graft damage.
  - Liver biopsy, HVPg measurement or TE are useful tools to assess graft damage and should be part of the follow-up protocol of these patients

#### ❖ HBV Infection

- Recurrence of HBV infection is defined as reappearance of HBsAg in serum plus quantifiable concentrations of HBV DNA
- Prediction of risk of HBV recurrence is dictated by level of HBV-DNA at time of LT
- Prevent recurrence of HBV infection with HBIG, and use NUCs (entecavir or tenofovir) to control recurrent HBV infection

| Donor       | Recipient                | Give HBIG for Immunoprophylaxis |
|-------------|--------------------------|---------------------------------|
| ○ Anti-HBc+ | – Anti-HBc- / anti-HBs-  | Yes                             |
|             | – Anti-HBc +/- anti-HBs+ | Yes                             |
|             | – Anti-HBc +/- anti-HBc+ | Yes                             |
|             | – HBsAg-                 | No                              |

#### ❖ Post-LT HBV Infection

- Combination of HBIG and NUCs is an effective strategy to prevent HBV recurrence in most HBV-infected patients undergoing LT (Grade I)
- Patients with undetectable HBV DNA at the time of LT and no history of resistance to NUCs are the best candidates to use low dose HBIG or a short course of HBIG (1-3 months) followed by NUC monotherapy
- Monotherapy with entecavir or tenofovir appears to be efficacious in controlling infection recurrence, but is probably not sufficient to prevent HBV graft infection
- Prophylaxis of HBV recurrence in patients who received a liver from an anti-HBc positive donor should be initiated immediately after LT if recipients do not have anti-HBs
- Lamivudine monotherapy is the best cost-effective treatment.
  - HBIG should not be used in patients HBsAg negative, who received a liver from an anti-HBc positive donor

"Optimism is the faith that leads to achievement.  
Nothing can be done without hope and confidence."

Helen Keller





## ❖ Alcoholic Liver Disease

- There is a highly variable rate of alcohol relapse in post-LT persons with alcoholic liver disease, but the drinking is heavy and harmful in only 10 – 20%, and results in ↓ survival, particularly after 10 yr of follow up. The patient must be encouraged to stop smoking and to exercise.

- All patients with a prior diagnosis of alcoholic liver disease should be encouraged to remain abstinent from alcohol after LT
- In the case of relapse into regular alcohol consumption patients should enter psychiatric treatment or counselling
- Specialist follow-up is relevant to assess alcohol abuse after LT, since harmful drinking, though not very frequent, is associated with decreased patient survival

### Prognosis

- Even though no clear correlation has been found between aetiology of liver disease and returning to work after LT, special attention should be devoted to patients transplanted for alcoholic liver disease, as they seem to be at higher risk of unemployment

## ❖ Non-Alcoholic Fatty Liver Disease (NAFLD)

- NAFLD / NASH may recur or develop de novo after LT for NASH (non-alcoholic steatohepatitis)
  - Corticosteroids may induce hyperglycemia and need to be minimized

- Prophylaxis of HBV recurrence in patients who received a liver from an anti-HBc positive donor should be initiated immediately after LT if recipients do not have anti-HBs
- Lamivudine monotherapy is the best cost-effective treatment.
  - HBIG should not be used in patients HBsAg negative, who received a liver from an anti-HBc positive donor



- Liver biopsy may be required to confirm recurrent or de novo NAFLD/NASH and to exclude other causes of elevated biochemical liver tests (Grade III)
- Prevention and treatment of NAFLD and NASH in LT recipients
  - Avoid excessive weight gain and control diabetes, dyslipidaemia and arterial hypertension

#### ❖ Recurrence of Diabetic Liver Disease

- AIH, PBC, PSC can recur in ~ ¼ of patients post-LT, but the recurrent disease is usually mild and does not alter the survival of the graft or the host.

#### ❖ Hepatocellular Cancer (HCC)

- Recurrence of HCC occurs in ~10% of recipients
  - Usually in the first 2 yr post-LT
  - Usually very aggressive with systemic dissemination of HCC (median survival < 1 yr)

#### ❖ Renal Dysfunction

- Within 6 mon of LT, > 50% of patients develop renal dysfunction, with about 50% of these developing stage ¾ chronic renal disease, and within 10 yr ~5% require renal replacement therapy (dialysis) / renal transplantation.
- The renal dysfunction may be present before or after LT and is often (> 70%) due to the post-LT use of calcineurins (CNIs).
- Treatment regimens to prevent acute graft rejection should include CNI minimization as well as regular long-term monitoring of serum creatinine ( $Cr_s$ ) / estimated creatinine clearance (eCC)

#### ❖ Infections

- Timing
  - First month
    - Nosocomial and post-operative infections
  - 2 – 6 mon
    - Opportunistic
    - Reactivation of latent infections
  - > 6 mon
    - Community acquired



- Site
    - Surgical site
      - ↑ morbidity
    - Abdominal cavity
      - ↑ mortality / ↑ loss of graft
    - Bladder
    - Blood
  - ❖ Bacterial
    - Gram-negative
      - Escherichia coli
      - Enterobacter
      - Pseudomonas
  - ❖ Viral
    - Cytomegalovirus (CMV)
      - Colitis
      - Hepatitis
      - ↓ bone marrow
- |   |         |
|---|---------|
| } | Viremia |
|---|---------|
- 
- |                                                                                           |                                                                                                                                                                                                                                                                                                                                                |                                                                                           |   |                                                                                    |
|-------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------|---|------------------------------------------------------------------------------------|
| - Prevention                                                                              | <ul style="list-style-type: none"> <li>▪ CMV+ donor → CMV+ recipient</li> <li>▪ CMV- → CMV-</li> </ul>                                                                                                                                                                                                                                         |                                                                                           |   |                                                                                    |
| - Treatment                                                                               | <table border="0"> <tr> <td style="vertical-align: top;"> <ul style="list-style-type: none"> <li>▪ Ganciclovir</li> <li>▪ Valganciclovir</li> </ul> </td> <td style="vertical-align: middle;">}</td> <td style="vertical-align: top;"> <ul style="list-style-type: none"> <li>▪ Viremia</li> <li>▪ CMV disease</li> </ul> </td> </tr> </table> | <ul style="list-style-type: none"> <li>▪ Ganciclovir</li> <li>▪ Valganciclovir</li> </ul> | } | <ul style="list-style-type: none"> <li>▪ Viremia</li> <li>▪ CMV disease</li> </ul> |
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- CMV prophylaxis for at least 3 months should be used in patients at a higher risk of developing CMV infection
- PTLD should always be suspected in liver transplanted patients, especially those at high risk
  - Presenting with fever, weight loss, night sweats, and even in the absence of lymphadenopathy
- Oral prophylaxis against Candida species is recommended during the first months, as it reduces mortality due to fungal infection
- Prophylaxis against Aspergillus is only recommended in high risk situations
- Prophylaxis against P. jirovecii with trimethoprim-sulphamethoxazole should be given to all liver transplanted patients for 6-12 months (Grade II-2)
- Treatment of P. jirovecii infection consists of trimethoprim-sulphamethoxazole. Corticosteroids are useful as adjunctive therapy to both reduce pulmonary inflammation and reduce post-infection fibrosis
- Patients undergoing treatment for tuberculosis should be monitored for potential hepatotoxicity and for acute rejection



- Epstein Barr Virus (EBV)
  - Associated with development of post-transplant lymphoproliferative disorder (PTLD)
    - Fever
    - Night sweats
    - ↓ body weight
    - Lymphadenopathy
  - EBV viremia → suspicion of PTLD → perform diagnostic imaging
  - Treatment
    - Immunosuppression (if possible )
    - Multidisciplinary team
      - Chemotherapy
      - Rituximab
      - Radiotherapy
      - Surgery
- HEV
  - Causes graft hepatitis / dysfunction
  - Patient often from “Central” Europe

#### ❖ Fungal

##### ➤ Risk factors

- Liver
  - Cold ischemia time
  - Rejection
  - Retransplantation
  - Portal vein thrombosis (PVT)
- Surgery
  - Short LT operative time
  - Intraoperative blood transfusion
  - Roux-Y biliary anastomosis
- Dialysis
  - Need for renal replacement therapy

##### ➤ Invasive disease must be distinguished from non-invasive infection

##### ➤ Types

- Candida albicans and non-albicans species
  - Fluconazole po for 1 mon post-LT for prophylaxis against invasive infection, such as fungemia or peritonitis
- Aspergillus
  - Commonest site
  - ↑ risk of fungemia
    - Lungs → CNS
    - Before LT, use of corticosteroids
    - During LT, intraoperative blood transfusion
    - After LT
      - Acute kidney / liver failure
      - Surgical re-exposure



- Treatment
  - Moderate risk
    - Amphotericin B, inhaled
  - High risk
    - MICA-fungin
- *Pneumocystis jirovecii*
  - Prevention
    - Trimethoprim-sulfamethoxazole for 6-12 mon
    - If allergy to sulfa drugs, use pentamidine
  - Treatment
    - TMP-SMX, plus
    - Corticosteroids, to
      - ↓ lung inflammation, and to
      - ↓ post-infection fibrosis
- Mycobacteria
  - Usually diagnosed in first year after LT
  - Presentation
    - Pulmonary
    - Extrapulmonary / atypical
  - Latent TB
    - Positive PPD skin test
    - Compatible chest X-ray
    - History of untreated TB

} Isoniazid, plus  
pyridoxine (vitamin B6)  
for 9 mon
  - Active TB
    - Severe
      - Rifampin
    - Non-severe
      - Isoniazid plus pyridoxine (or levofloxacin) and ethambutol

### Metabolic Syndrome

- About ½ of post-LT patient develop
  - Diabetes mellitus
  - Metabolic syndrome
  - Dyslipidemia
  - Hypertension (arterial)

} ↑ cardiovascular disease and deaths
- Careful management of risk factors is important

#### Clinical Therapeutic Reminder

- CNIs and statins interact by their common metabolism by CYP450 3A4 → ↑ statin concentration → rhabdomyolysis



- Efficacious and prompt treatment of modifiable risk factors in the form of lifestyle changes, pharmacological therapies and modifications of the immunosuppression is imperative to prevent serious cardiovascular complications
- Various pharmacological therapies must be initiated as soon as possible to control arterial hypertension, hyperlipidemia, diabetes and obesity
- A healthy diet and regular exercise programs represent additional effective management options

### Bone Disease

- Loss of bone and ↑ risk of bone fracture in first 6 mon post LT, which then slows after 1 yr
- DEXA Scan showing ↓ bone mineral density / osteoporosis
  - Calcium and vitamin D
  - Bisphosphonates
  - Exercise, weight bearing

- Bone mineral density screening should be performed yearly for patients with pre-existing osteoporosis and osteopenia and every 2-3 years in patients with normal bone mineral density.
  - Thereafter, screening depends on the progression of changes in bone mineral density and on risk factors
- LT patients with osteopenia should perform regular weight-bearing exercise and receive calcium and vitamin D supplementation (Grade II-3)
- Bisphosphonate therapy should be considered in patients with osteoporosis or recurrent fractures

### De Novo Malignancies

#### ➤ ↑ risk

- |                                                                                                                                                                                                     |   |                                                                                                                                  |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---|----------------------------------------------------------------------------------------------------------------------------------|
| <ul style="list-style-type: none"> <li>○ Lymphoproliferative malignancies (30x↑)</li> <li>○ Skin (non-melanomas: squamous cell, basal cell (20x↑)</li> <li>○ Solid organ cancers (2-3x↑)</li> </ul> | } | <p>~20% at 10 yr</p> <ul style="list-style-type: none"> <li>– Poor prognosis</li> <li>– Median survival post-LT, 3 yr</li> </ul> |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---|----------------------------------------------------------------------------------------------------------------------------------|



➤ Causes / associations

- Immunosuppressive drugs
- Viral infections
  - EBV
  - PTLD
  - HPV
  - HBV
- Liver disease
  - Precirrhotic / cirrhotic
  - PSC plus UC (primary biliary sclerosis and ulcerative colitis)
- Habits / lifestyle
  - Alcohol abuse
  - Smoking
    - ↑↑ risk of
      - Oropharyngeal-laryngeal
      - Lung cancer

Malignancy

- Risk of de novo malignancy should be considered with Tac or CsA-based immunosuppressive regimens
- The risk of malignancy related to CNIs in clinical practice may come from the dosage rather than the type of CNI used
- No evidence suggesting a link between the use of MMF and de novo malignancy after LT
- There are no published RCTs evaluating the effect of mTOR inhibitors in preventing nor treating de novo malignancy after LT

Cancer Screening

- Efficacious and prompt treatment of modifiable risk factors in the form of lifestyle changes, pharmacological therapies and modifications of the immunosuppression is imperative to prevent serious cardiovascular complications
- Various pharmacological therapies must be initiated as soon as possible to control arterial hypertension, hyperlipidemia, diabetes and obesity
- A healthy diet and regular exercise programs represent additional effective management options



## Quality of Life (QoL)

- QoL is important to monitor and to enhance
- Treat associated depression, anxiety
- Improved sexual function in men and women post-LT
- Improvement in menstruation and fertility
- Pregnancy
  - Avoid for 6 – 12 mon post-LT
  - Continue immunosuppression maintenance during pregnancy, except for MMF
    - To paraphrase, do **not** use MMF in pregnancy
  - Use barrier methods for contraception
  - ↑ risk of need for caesarean section
  - Avoid breastfeeding

- Physical activity in liver transplant recipients should be proposed as part of their therapeutic regimens

- Quality of life after LT should always be considered as an outcome measure

## Mental Health

- Physical and psychosocial functions after LT should be properly assessed in adolescent liver transplant recipients as they are typically lower compared to the general population
- Adherence to medical prescriptions and particularly to immunosuppressive therapy should always be evaluated after LT.
  - Special attention should be posed on immunosuppression-related physical side effects as they represent the major reason for non-adherence among adolescent recipients
  - A specific structured support should be planned in transplanted children and adolescents concerning schooling
  - Multidisciplinary measures developed by professional educators, supported by psychologists, and coordinated by physicians are warranted to improve adherence before and after LT





- Give the effect of pregnancy on the fetus and the mother with LT.
  - Baby
    - ↑ loss, prematurity, ↓ birth weight
  - Mother
    - Hypertension / preeclampsia
    - Gestational diabetes
    - Graft dysfunction

#### Pregnancy

- LT patients of reproductive age should always be counselled about the possibility of pregnancy and the use of contraception
- Pregnancy should be avoided for the first 12 months after transplantation (some centres advocate waiting 24 months)
- Immunosuppression should be maintained during pregnancy.
  - Steroids, CNIs and azathioprine have not been reported to be teratogenic
  - Mycophenolate mofetil and azathioprine are usually **not** recommended
- mTOR inhibitors may affect spermatogenesis in male recipients

“Mediocrity is metric modulation, bringing people  
back (regression) to the mean.”

Grandad



## UPDATED GUIDELINES ON AUCTE LIVER FAILURE (ALF): AGA GUIDELINES

Abbreviations: AGA, American Gastroenterology Association

Flamm SL, et al. Gastroenterol 2017; 152:644-647.

- Testing
  - HSV
  - HEV in pregnancy
  - Cu<sup>2+</sup> serum, liver, urine (24 hr)
  - Serum ceruloplasmin
  - VZV
  - Liver biopsy

}

}

}

Recommendation

High negative predictive value

Not recommended
- Assessment
  - MELD score
- Treatment
  - N-acetyl cysteine (NAC) for acetaminophen toxicity
    - Yes
  - Not for acetaminophen toxicity
    - Not recommended but does benefit patients with HE stage 1 or 2, so may be considered (author's personal suggestion)
  - Empiric treatments to
    - ↓ intracranial pressure (ICP)
    - Extracorporeal artificial liver support (ECALS) (use only within context of a clinical trial)

Abbreviations: Cu<sup>2+</sup>, copper; ECALS, extracorporeal artificial liver support; HE, hepatic encephalopathy; HEV, hepatitis E virus; HSV, herpes simplex virus; ICP, intracranial pressure; MELD, Model for end-stage liver disease; NAC, N-acetyl cysteine; VZV, varicella zoster virus



## **COCHRANE COLLABORATION**

### **Analyses in GI / Hepatology**



## ESOPHAGUS

### Achalasia

- Endoscopic pneumatic dilation (EPD) versus botulism toxin injection (BTX) in the management of primary achalasia
  - EPD is as effective as BTX at 4 wks post-treatment, but
    - EPD is superior to BTX at 6 and 12 mon
      - RR 1.57 95% CI 1.19 to 2.08, P = 0.0015

Leyden JE, et al. Cochrane Library. Cochrane Database of Systemic Reviews 2014; 12. Art.No: CD005046. ([www.cochranelibrary.com](http://www.cochranelibrary.com))

### GERD Treatment

- Laparoscopic fundoplication [LFP] surgery versus medical management [MM] for gastroesophageal reflux disease (GERD) in adults
  - The 571 participants in 4 RCTS
    - Had experience reflux symptoms for  $\geq 6$  mon despite long-term acid suppressive therapy
    - Were suitable for surgical intervention, if randomized to this study arm
  - The laparoscopic fundoplication (LFP) group was inferior to medical management (MM) in
    - Heartburn
      - Short term
        - RR 0.45, 95% CI 0.30 to 0.49; 1 study, 554 participants,
      - Medium term
        - RR 0.19, 95% CI 0.10 to 0.34; 1 study, 554 participants
      - Long-term
        - RR 0.56, 95% CI 0.44 to 0.72; 1 study, 217 participants
    - Reflux symptoms
      - Short term
        - RR 0.10, 95% CI 0.05 to 0.24; 1 study, 554 participants
      - Medium term
        - RR 0.15, 95% CI 0.06 to 0.35; 1 study, 554 participants
      - Long-term
        - RR 5.36, 95% CI 2.1 to 13.64; 1 study, 554 participants
    - Development of serious adverse effects
      - RR 1.46; 95% CI 1.01 to 2.11; 2 studies, 637 participants
    - Dysphagia
      - Short term
        - RR 3.58, 95% CI 1.01 to 2.11; 2 study, 637 participants
      - Medium term
        - RR 0.19, 95% CI 0.10 to 0.34; 1 study, 554 participants
      - Long-term
        - RR 0.56, 95% CI 0.44 to 0.72; 1 study, 217 participants



- The only category in which LFP was superior to long-term MM was in the short term and with one of the two (HRQoL, health-related quality of life) scores
  - GERD-specific QoL
    - SMD 0.58, 95% CI 0.46 to 0.70; 11160 participants, 4 studies

Abbreviations: APC, argon plasma coagulation; BTX, botulism toxin injection; CI, confidence interval; GERD, gastroesophageal reflux disease; HRQoL, health-related quality of life; LFP, laparoscopic fundoplication; MD, mean difference; MM, medical management; QoL, quality of life; RCT, randomized controlled trial; RR, relative risk; SEMS, self-expanding metal stent; SMA, standardized mean differences; TCAT, thermal and chemical ablation therapy

Garg SK and Gurusamy KS. Cochrane Library. Cochrane Database of Systemic Reviews 2015; 11. Art.No: CD003243. ([www.cochranelibrary.com](http://www.cochranelibrary.com))

## Esophageal Cancer

- Interventions for dysphagia in esophageal cancer
  - Self-expanding metal stent (SEMS) insertion was superior to plastic tube insertion (PTI) in 53 RCTs, and 3684 persons
  - Thermal and chemical ablative therapy (TCAT; laser, photodynamic therapy [PDT], injection of ethanol):
    - Comparable in effectiveness to SEMS
    - Comparable adverse effects
    - ↑ requirement for re-interventions
    - ↑ adverse effects compared to SEMS and
  - Niti-S (double-layered nitinol) versus Niti-S simple
    - ↑ survival
    - ↓ complications
  - Bradytherapy superior to SEMS
    - ↑ survival
    - ↓ complications
    - ↑ quality of life

Sreedharan A, et al. Cochrane Library. Cochrane Database of Systemic Reviews 2011; 2. Art.No: CD005048. ([www.cochranelibrary.com](http://www.cochranelibrary.com))

- Preoperative chemotherapy for resectable thoracic esophageal cancer (ECA)
  - Preoperative chemotherapy
    - ↑ overall survival
      - HR 0.88, 95% CI 0.80 to 0.96 (13 RCTs, 2362 participants)
    - ↑ rate of complete (R<sub>0</sub>) resection
      - RR 1.11, 95% CI 1.03 to 1.19
  - The benefit of preoperative chemotherapy
    - Did not change
      - Rate of resection
      - Recurrence of ECA
      - Non-fatal complications



- Did ↑
  - Toxicity
  - Preoperative mortality

Kidane B, et al. Cochrane Library. Cochrane Database of Systemic Reviews 2015; 5. Art.No: CD001556. ([www.cochranelibrary.com](http://www.cochranelibrary.com))

- Laparoscopic (LAP) versus open transhiatal esophagectomy (OTE) for esophageal cancer (ECA)
  - LAP superior to OTE
    - Short/long-term mortality
    - Anastomotic stenosis
    - Short/long-term recurrence

Gurusamy KS, et al. Cochrane Library. Cochrane Database of Systemic Reviews 2016; 3. Art.No: CD011390. ([www.cochranelibrary.com](http://www.cochranelibrary.com))

- Non-surgical versus surgical treatment for esophageal cancer in patients with esophageal squamous cell cancer who respond to induction chemoradiotherapy, and who are fit for surgery
  - Long-term mortality
    - No difference between chemoradiotherapy (CRT) and surgery (surg) (8 trials, 1132 participants)
    - Higher in radiotherapy than surgery
      - HR 1.39, 95% CI 1.18 to 1.64 (3 studies, 512 participants, but risk of bias and random errors)
  - Recurrence rates
    - Short term CRT = Surg
    - Long-term CRT = Surg
  - Adverse effects
  - Quality of life
    - Short term CRT > Surg

Best LMJ, et al. Cochrane Library. Cochrane Database of Systemic Reviews 2016; 3. Art.No: CD011498. ([www.cochranelibrary.com](http://www.cochranelibrary.com))

- Chinese Herbal Medicine for esophageal cancer
  - Adding traditional Chinese (herbal) medicine (TCM) to treatment with radiotherapy or chemotherapy for esophageal cancer
    - ↑ quality of life
      - More improvement
        - RR 2.20, 95% CI 1.42 to 3.39 (5 RCTs, 233 participants)
      - Less deterioration
        - RR 0.41, 95% CI 0.27 to 0.62 (6 RCTs, 287 participants)



- ↓ adverse effects
  - Radiation esophagitis
    - RR 0.66, 95% CI 0.47 to 0.94 (2 RCTs, 287 participants)
  - GI reactions
    - RR 0.54, 95% CI 0.36 to 0.81 (4 RCTs, 90 participants)
  - WBC
    - RR 0.60, 95% CI 0.44 to 0.83 (4 RCTs, 224 participants)

Chen X, et al. Cochrane Library. Cochrane Database of Systemic Reviews 2016; 1. Art.No: CD004520. ([www.cochranelibrary.com](http://www.cochranelibrary.com))

- Chemotherapy versus chemotherapy plus surgery for esophageal cancer (93% squamous, 7% adenocarcinoma) patient population esophageal cancer
 

|                                   |   |                                        |
|-----------------------------------|---|----------------------------------------|
| Squamous 97%<br>Adenocarcinoma 7% | } | Stage ≥ T3 and/or positive lymph nodes |
|-----------------------------------|---|----------------------------------------|

  - Adding esophagectomy to chemoradiotherapy
    - Little or no diffuse or overall survival HR 0.99, 95% CI 0.79 to 1.24, P = 0.92
    - ↓ locoregional relapse
      - HR 0.55, 95% CI 0.39 to 0.76; P = 0.004 (2 RCTs, 431 participants)
    - ↓ need for salvage procedures for dysphagia
      - HR 0.52, 95% CI 0.36 to 0.74
    - ↑ treatment-related mortality
      - RR 5.11, 95% CI 1.74 to 15.02; P = 0.003, but low quality evidence
    - ↓ short term QoL MD 0.93, 95% CI 0.24 to 1.62

Vellayappan BA, et al. Cochrane Library. Cochrane Database of Systemic Reviews 2017; 8. Art.No: CD010511. ([www.cochranelibrary.com](http://www.cochranelibrary.com))

## Esophagogastric Cancer

- Long-term proton pump inhibitor (PPI) use and the development of gastric pre-malignant lesions
  - Although results were considered to be imprecise , this systemic review concluded that there is "...no clear evidence that the long-term use of PPIs can cause or accelerate the progression of corpus gastric atrophy or intestinal metaplasia.
    - Corporal atrophy PPI use long-term (maintenance) versus non-use OR 1.50, 95% CI 0.59 to 3.80; P = 0.39 (4 RCTs, 1070 participants)
    - Corporal intestinal metaplasia OR 1.46, 95% CI 0.43 to 5.03; P = 0.55 (5 RCTs, 1408 participants)
  - Long-term PPI maintenance was associated with ↑ risk of ECL hyperplasia
    - Focal (linear/micronodular)
      - OR 3.98, 95% CI 1.31 to 12.16; P = 0.02 (6 RCTs, 1705 participants)
    - Diffuse (linear simple)
      - OR 5.01, 95% CI 1.54 to 16.26; P = 0.007 (6 RCTs, 1705 participants)



- Give the Correa cascade of multi-step gastric carcinogenesis.
  - Normal gastric mucosa → chronic gastritis → atrophic gastritis → intestinal metaplasia → dysplasia → gastric carcinoma
    - It is important to identify factors which may cause or accelerate this process
    - This Correa cascade is seen in persons with an infection with *H. pylori*, which is itself considered to be a carcinogen
    - This systemic review does **not** support the suggestion that PPI ↑ risk of developing corporal atrophic gastritis or intestinal metaplasia, but it is important to note that in this review the participants were not stratified for presence of an *H. pylori* infection.

Song H, et al. Cochrane Library. Cochrane Database of Systemic Reviews 2014; 12. Art.No: CD010623. ([www.cochranelibrary.com](http://www.cochranelibrary.com))

## Dysphagia

- Percutaneous endoscopic gastrostomy (PEG) versus percutaneous radiological gastrostomy (PRG) for swallowing disturbances
  - The authors “...identified no RCTs comparing PEG versus PRG in persons with swallowing disturbances.”

Yuan Y, et al. Cochrane Library. Cochrane Database of Systemic Reviews 2016; 2. Art.No: CD009198. ([www.cochranelibrary.com](http://www.cochranelibrary.com))

- Botulinum toxin for upper esophageal sphincter dysfunction in neurological disorders.
  - In persons with acute neurological disease arising from dysfunction of the upper esophageal sphincter, there are no RCTS and thus “...no clear consensus on ulceration botulinum toxin is safe and effective.”

Regen J, et al. Cochrane Library. Cochrane Database of Systemic Reviews 2014; 5. Art.No: CD009968. ([www.cochranelibrary.com](http://www.cochranelibrary.com))

## Esophagectomy

- Omentoplasty surgery for early-stage esophageal cancer (ECA) is esophagectomy followed by esophagogastronomy (EGG)
- Esophagectomy plus EGG increases the risk of anastomotic leakage
- The addition of omentoplasty to EGG
  - ↓ risk of anastomotic leakage RR 0.25, 95% CI 0.11 to 0.55
  - Had no benefit with regards to other surgery-related complications
- This benefit is present for transhiatal, transthoracic or three-field esophagectomy
  - ↓ duration of hospitalization MD -2.13, 95% CI -3.57 to -0.69

Yuan Y, et al. Cochrane Library. Cochrane Database of Systemic Reviews 2014; 10. Art.No: CD008446. ([www.cochranelibrary.com](http://www.cochranelibrary.com))





## STOMACH

### Dyspepsia

- Deprescribing versus continuation of chronic proton pump inhibitor use in adults
  - It is estimated that ~25% to 70% of persons are prescribed a PPI “inappropriately”
  - Every effect needs to be made by the prescribed physician to periodically review the patient’s need to continue PPI therapy
  - Maintenance therapy with PPI is correctly indicated in some persons with dyspepsia, but in a attempt to reduce the risk of polypharmacy and the long-term risks of PPI therapy, the use of “on-demand” PPIs has been proposed for persons who had an EGD and respond symptomatically to PPIs.
  - This Cochrane review compares the clinical outcomes of continuous PPI use versus “deprescribing” PPIs.
  - In the on demand group versus continues PPI maintenance therapy (5 trials, 1653 participants), on-demand therapy was associated with
    - ↑ lack of symptoms control
      - RR 1.71, 95% CI 1.31 to 2.21
    - ↓ drug burden
      - MD -3.79, 95% CI -4.73 to -2.84
    - ↓ participants satisfaction, “...although heterogeneity was high”

Boghossian TA, et al. Cochrane Library. Cochrane Database of Systemic Reviews 2017; 3. Art.No: CD011969. ([www.cochranelibrary.com](http://www.cochranelibrary.com))

### Functional Dyspepsia

- Proton pump inhibitors for functional dyspepsia [FD]
  - Uninvestigated dyspepsia patients have not had an esophagogastroduodenoscopy (EGD) investigation into the course(s) of their symptoms, whereas persons with dyspepsia and a normal EGD may be said to have functional dyspepsia.
    - Persons with dyspepsia plus a normal EGD may be subdivided into further groups by using additional testing, such as esophageal pH or manometric studies
    - For the purpose of this systemic review, functional dyspepsia was defined as “... continuous or frequently recurring epigastric pain or discomfort for which no organic cause can be found...” by EGD.
  - PPIs are
    - Effective for the relief of dyspepsia from FD, independent of the dose and duration of treatment, as composed with placebo
      - RR 0.88, 95% CI 0.82 to 0.94 (18 studies, 6172 participants; NNTB 11)
    - Slightly more effective than prokinetics
      - RR 0.89, 95% CI 0.81 to 0.99 (5 studies, 1033 participants, NNTB 16)
    - Equivalent to the use of H2RAs, or PPI plus prokinetics
      - H2RA
        - RR 0.88, 95% CI 0.74 to 1.04 (2 studies, 740 participants)
      - PPI plus prokinetics (PK)
        - RR 0.85, 95% CI 0.68 to 1.08 (2 studies, 407 participants)



- There was no difference in subgroups
  - Country of origin
  - H. pylori status
  - Reflux symptoms
  - Rome III subtypes
- Adverse effects
  - PPIs no different than H2RA or PKs
  - PPIs had more adverse effects than did PPI plus PK
    - RR 0.60, 95% CI 0.39 to 0.93 (2 studies, 407 participants)

Abbreviations: NNTB, number needed to treat an additional beneficial outcome

Pinto-Sanchez MI, et al. Cochrane Library. Cochrane Database of Systemic Reviews 2017; 11. Art.No: CD011194. ([www.cochranelibrary.com](http://www.cochranelibrary.com))

### Upper Gastrointestinal Bleeding

- Vitamin K use for upper GI bleeding (UGIB) in people with liver diseases
  - “We cannot recommend or refute use of vitamin K for upper gastrointestinal bleeding with liver diseases.”

Marti-Carvajal AJ and Sola I. Cochrane Library. Cochrane Database of Systemic Reviews 2015; 6. Art.No: CD004792. ([www.cochranelibrary.com](http://www.cochranelibrary.com))

- Anti-fibrinolytic amino acids for upper gastrointestinal bleeding in people with acute or chronic liver disease
  - “We cannot recommend or refute anti-fibrinolytic amino acids for upper gastrointestinal bleeding in people with acute or chronic liver disease.”

Marti-Carvajal AJ and Sola I. Cochrane Library. Cochrane Database of Systemic Reviews 2015; 6. Art.No: CD006007. ([www.cochranelibrary.com](http://www.cochranelibrary.com))

- Tranexamic acid for [non-variceal] upper gastrointestinal bleeding
  - The current standard of care for persons with acute non-variceal upper GI bleeding is ABC's stabilization including volume repletion and blood transfusion when hemoglobin concentration falls below 70, early endoscopy plus endoscopic hemostatic therapy for active arterial or venous bleeding, or the presence of a non-bleeding visible vessel.
  - Previous reviews have reported that tranexamic acid (an anti-thrombolytic agent) may reduce the patient's mortality rate.
  - This systemic review concurs that tranexamic acid (TA) may ↓ mortality in persons with upper GI bleeding: comparing the TA versus the control groups, the use of TA was associated with
    - ↓ mortality
      - RR 0.60, 95% CI 0.42 to 0.87, P = 0.007 (8 RCTs, 1701 participants)
  - Note that this reduction in mortality was lost"...
    - When all participants in the intervention [TA] group with missing outcome data were included as treatment failures, or
    - When the analysis was limited to trials with low nutrition bias



- ↓ rebleeding (trend only)
  - RR 0.80, 95% CI 0.64 to 1.00, P = 0.07
- ↓ surgery
  - RR 0.73, 95% CI 0.56 to 0.95, fixed-effect meta-analysis, but significance lost when using a random-effects meta-analysis (RR 0.61, 95% CI 0.35 to 1.04, P = 0.07)

Bennett C, et al. Cochrane Library. Cochrane Database of Systemic Reviews 2014; 11. Art.No: CD006640. ([www.cochranelibrary.com](http://www.cochranelibrary.com))

## Peptic Ulcer Disease

- Medical versus Surgical Treatment for Refractory or Recurrent Peptic Ulcer

“We found no studies that provided the relative benefits and harms of medical versus surgical treatment for recurrent or refractory peptic ulcers.”

Gurusamy KS and Pallari E. Cochrane Library. Cochrane Database of Systemic Reviews 2016; 3. Art.No: CD011523. ([www.cochranelibrary.com](http://www.cochranelibrary.com))

## Nutrition

- Percutaneous endoscopic gastrostomy (PEG) versus nasogastric tube (NGT) for adults with swallowing disturbances
  - Primary outcome
    - Interventions failure lower with PEG than with NGT
      - RR 0.18, 95% CI 0.005 to 0.59; 8 studies, 408 participants
    - “Pull” subgroup superior to “push” PEG technique
      - RR 0.07, 95% CI 0.01 to 0.35, 3 studies, 90 participants
  - Secondary outcomes
    - Intervention favoured PEG versus NET
      - Quality of life
      - Inconvenience
        - RR 0.03, 95% CI 0.00 to 0.29
      - Discomfort
        - RR 0.03, 95% CI 0.00 to 0.29
      - Alter body image
        - RR 0.01, 95% CI 0.00 to 0.18
      - Social activities
        - RR 0.01, 95% CI 0.00 to 0.18
    - Interventions PEG versus NET not sufficiently different
      - Mortality
      - Any adverse events or specific adverse events
      - Improvement in nutrition status

Gomes JR, et al. Cochrane Library. Cochrane Database of Systemic Reviews 2015; 5. Art.No: CD008096. ([www.cochranelibrary.com](http://www.cochranelibrary.com))



## H. pylori

- Periodontal therapy as adjunctive treatment for gastric *Helicobacter pylori* infection
  - Periodontal therapy consists of “procedures carried out to support the health of the structure in the mouth...and includes oral hygiene instruction, tooth brushing, the use of mouthwash, and professional removal of dental plaque and tartar from the teeth and gum line.”
  - Periodontal therapy
    - ↑ efficacy of *H.pylori* eradication with antibiotics, compared with eradication therapy alone
      - OR 2.15, 95%CI 1.47 to 3.14,  $P < 0.0001$  (7 RCT studies, 691 participants)
    - ↑ non-recurrence (↓ recurrence) rate of *H. pylori* infection
      - OR 3.60, 95%CI 2.11 to 6.15,  $P < 0.00001$

Ren Q, et al. Cochrane Library. Cochrane Database of Systemic Reviews 2015; 5. Art.No: CD009477. ([www.cochranelibrary.com](http://www.cochranelibrary.com))

- Sequential versus standard triple first-line therapy for *Helicobacter pylori* eradication
  - Sequential treatment (SEQ) with PPI plus amoxicillin (PPI + A) for 5 days and then followed by 5 days of standard triple therapy (STT) comprising PPI plus clarithromycin plus metronidazole (PPI + CM) for 5 days has been used with some success when first-line treatment of an *H.pylori* infection has failed (STT → SEQ).
  - First-line therapy with SEQ has been compared with first-line STT in adult and children diagnosed as positive for *H. pylori* infection and naïve to *H. pylori* treatment.

- First line therapy of *H. pylori* infection with SEQ is
    - Overall superior to STT 82% versus 75% (intention-to-treat)
      - RD 0.09. 95% CI 0.06 to 0.11,  $P < 0.001$  (44 RCTs, 12,284 participants)
  - When STT is given for 14 days
    - In participants with clarithromycin-resistance of their *H. pylori*, the average efficacy of SEQ was 75% versus 43% with STT

About 1 in 5 persons in each treatment group repeated adverse effects.

Nyssen OP, et al. Cochrane Library. Cochrane Database of Systemic Reviews 2016; 3. Art.No: CD011389. ([www.cochranelibrary.com](http://www.cochranelibrary.com))



## Gastric Cancer

- Laparoscopic versus open gastrectomy for gastric (GCA)
  - In persons with non-metastatic gastric cancer, the only surgical option for these potentially curable patients and laparoscopic versus open gastrectomy (LG and OG, respectively)
  - "... there is no difference in short or long-term outcomes between LG versus OG, including
    - 30 day post-operative mortality, recurrence, positive margins lymph nodes resected, blood transfusions, or length of hospital stay

Best LMJ, et al. Cochrane Library. Cochrane Database of Systemic Reviews 2016; 3. Art.No: CD011389. ([www.cochranelibrary.com](http://www.cochranelibrary.com))

- Diagnostic accuracy of endoscopic ultrasonography (EUS) for the preoperative locoregional staging of primary gastric cancer

EUS has a role in routine clinical practice to determine primary tumor depth (T-stage) and regional lymph node status (N-stage) in persons with primary gastric cancer (index test, EUS; reference standard, pathology evaluation; primary carcinoma of the stomach, target condition).

- Performance characteristics of EUS in discriminating

### Versus T3/T4 advanced

|                                                                         |                           |   |                               |
|-------------------------------------------------------------------------|---------------------------|---|-------------------------------|
| – T1/T2 superficial                                                     |                           |   |                               |
| ▪ Sensitivity                                                           | 0.86, 95% CI 0.81 to 0.90 | } | 50 studies, 4397 participants |
| ▪ Specificity                                                           | 0.90, 95% CI 0.87 to 0.93 |   |                               |
| – T1 early gastric cancer (EGCA) versus T2 (muscle-infiltrating tumors) |                           |   |                               |
| ▪ Sensitivity                                                           | 0.85, 95% CI 0.78 to 0.91 | } | 46 studies, 2742 participants |
| ▪ Specificity                                                           | 0.90, 95% CI 0.85 to 0.93 |   |                               |
| – T1a (mucosal) versus T1b (submucosal)                                 |                           |   |                               |
| ▪ Sensitivity                                                           | 0.87, 95% CI 0.81 to 0.92 | } | 20 studies, 3321 participants |
| ▪ Specificity                                                           | 0.75, 95% CI 0.62 to 0.84 |   |                               |
| – Metastatic involvement of lymph nodes                                 |                           |   |                               |
| ▪ Sensitivity                                                           | 0.83, 95% CI 0.79 to 0.87 | } | 44 studies, 3573 participants |
| ▪ Specificity                                                           | 0.67, 95% CI 0.61 to 0.72 |   |                               |

Mocellin S and Pasquali S. Cochrane Library. Cochrane Database of Systemic Reviews 2015; 2. Art.No: CD009944. ([www.cochranelibrary.com](http://www.cochranelibrary.com))

- Abdominal drainage versus no drainage post-gastrectomy for gastric cancer
  - For persons with resectable gastric cancer, gastrectomy remains the main therapy
    - An abdominal drain has been widely used in the past in conjunction with a gastrectomy
  - This systemic review found "... no convincing evidence to support routine drain use after gastrectomy for gastric cancer"



- No evidence for a difference between the 2 groups, drain versus no drain post gastrectomy (4 RCTs, 438 participants)
  - Time to start soft diet after surgery
  - Mortality
  - Re-operation
  - Post-operation complications
    - Pneumonia
    - Wound infection
    - Abdominal abscess
    - Anastomonic leak
- Of fact, the use of drain was disadvantage, since there were drain-related complications including
  - ↑ or time
    - MD 0.69 day, 95% CI 0.18 to 1.21
  - Length of hospital stay
    - MD 0.69 day, 95% CI 0.18 to 1.21

Wang Z, et al. Cochrane Library. Cochrane Database of Systemic Reviews 2015; 2. Art.No: CD008788. ([www.cochranelibrary.com](http://www.cochranelibrary.com))

- Molecular-targeted first line therapy for advanced gastric surgery
  - Surgery provides the only hope for cure of gastric cancer (GCA), but unfortunately most patients may not be surgical candidates, or have advanced or metastatic disease, and the only treatment left is the modestly effective radiotherapy or chemotherapy
  - Inhibitors of epidermal growth factor (EGFR) or of vascular endothelial growth factor (VEGF) are being used to treat advanced GCA.
    - This molecular-targeting may have a small benefit on (low quality evidence)
      - Mortality
        - HR 0.92, 95% CI 0.80 to 1.05 (10 studies)
      - Progression-free survival
        - HR 0.90, 95% CI 0.78 to 1.08
      - Tumor response to chemo-/radiotherapy
        - OR 1.24, 9% CI 1.00 to 1.55
    - The “cost” of these small benefit was
      - ↑ adverse events
        - OR 2.23, 95% CI 1.27 to 3.95 (5 trials, 2290 participants)
      - ↑ sever adverse events
        - OR 1.19, 95% CI 1.03 to 1.37 (8 trials, 3800 participant)

Song H, et al. Wang Z, et al. Cochrane Library. Cochrane Database of Systemic Reviews 2016; 7. Art.No: CD011461. ([www.cochranelibrary.com](http://www.cochranelibrary.com))



## SMALL BOWEL

### Acute Diarrhea

- Oral Zinc for treating diarrhea in children
- ❖ Support for the use of zinc supplementation in children with acute diarrhea (trials mostly conducted in Asian countries)
  - Children < 6 mon of age
    - No malnutrition
      - ↓ average duration of diarrhea by ~ ½ day
      - MD 11.46 hr, 95% CI 19.72 to 3.19 (2581 children, 9 trials)
      - Number of children whose diarrhea persists for 7 days
      - RR 0.73, 95% CI 0.61 to 0.88; 3865 children, 6 trials
    - With malnutrition
      - ↓ average duration of diarrhea by ~ 1 day
      - MD – 26.39 hr, 95% CI 36.54 to 16.23, 419 children, 5 trials
  - Children > 6 mon
    - With malnutrition
      - ↓ average duration
        - MD 15 & 4 hr, 95% CI 25.43 to 6.24, 529 children, 5 trials
      - Areas of high prevalence of malnutrition or zinc deficiency
      - The current evidence does not support the use of zinc supplementation

Lazzerini I and Wanzira H. Cochrane Library. Cochrane Database of Systemic Reviews 2016; 12. Art No: CD005436. ([www.cochranelibrary.com](http://www.cochranelibrary.com))

### Treating and Preventing Acute Diarrhea

Gregorio GV, et al. Cochrane Library. Cochrane Database of Systemic Reviews 2016; 12. Art No: CD006519.

- Polymer-based oral rehydration solution (ORS)
  - Glucose-based oral rehydration (ORS) should have an osmolarity < 270 mOsm/L
    - Rice- or wheat-based ORS may be superior to glucose-based ORS
- ❖ Osmolarity ≤ 250 (Osm < 270)
  - Polymer-based ORS (poly-ORS) vs glucose-based ORS (gb-ORS)
    - Superior
      - 24 hr ↓ stool output
        - MD -24.60 mL/kg; 95% CI -40.69 to -8.51 (1 trial, 99 participants)
      - Average duration
        - MD -8.24 hr; 95% CI -13.17 to -3.30 (5 trials, 364 participants)
    - No difference in risk of needing unscheduled use of IV fluid
      - RR 0.66; 95% CI 0.43 to 1.02 (4 trials, 376 participants)



- ❖ Osmolarity  $\geq 310$  (Osm  $> 310$ ) polymer-based ORS (poly-ORS) vs glucose-based ORS (gb-ORS)
  - Poly-ORS vs gb-ORS
    - Superior
      - 24 hr  $\downarrow$  stool output
        - MD -65.47 mL/kg; 95% CI -83.92 to -47.03 (16 trial, 1483 participants)
      - Average duration
        - MD -8.57 hr; 95% CI -13.17 to -4.03 (19 trials, 1877 participants)
      - Less need for IV fluids
        - RR 0.75; 95% CI 0.57 to 0.98
    - No difference in vomiting, hyponatremia, hypokalemia, or persistence of diarrhea

Bottom Lines:

- Polymer-based ORS is superior at 24 hr to glucose-based ORS in  $\downarrow$  24 hr stool output by  $\sim 25$  mL/kg and  $\downarrow$  average duration by  $\sim 8$  hr, both when the ORS osmolality was either  $< 250$  or  $> 310$  mOsm/L.

- Oral zinc in children

Lazzerini M and Wanzira H. Cochrane Library. Cochrane Database of Systemic Reviews 2016; 12. Art No: CD005436.

➤ Acute diarrhea

- ❖ Children  $> 6$  mon of age

- Shortens average duration of diarrhea
  - No malnutrition
    - MD -11.46; 95% CI -19.72 to -3.19
  - Malnutrition
    - MD -26.39; 95% CI -36.54 to -16.23
- Number of children with diarrhea persisting for 7 d
  - RR 0.73; 95% CI 0.61 to 0.88 (6 trials, 3865 children)
  - Malnutrition
- $\uparrow$  risk of vomiting
  - RR 1.57; 95% CI 1.32 to 1.86 (6 trials, 2605 children)

- ❖ Children  $< 6$  mon of age

- No effect on average duration of diarrhea
  - MD 5.23 hr; 95% CI -4.00 to 14.45 (2 trials, 1334 children)
- No effect on number of children with diarrhea persisting for 7 d (RR 1.24; 95% CI 0.99 to 1.54; 1 trial, 1074 children)
- $\uparrow$  risk of vomiting
  - RR 1.54; 95% CI 1.05 to 2.24 (2 trials, 1334 children)





➤ Persistent diarrhea

- Zn shortens average duration of diarrhea
  - MD -15.84 hr; 95% CI -25.43 to -6.24 (5 trials, 529 children)
- In children < 6 mon of age, oral zinc has no benefit
- In children > 6 mon of age and regardless of the child's nutritional status, oral zinc shortens the average duration of diarrhea and the proportion of children with diarrhea persisting for 7 d

▪ Hand washing to prevent diarrhea

Ejemot-Nwadiaro RI, et al. Cochrane Library. Cochrane Database of Systemic Reviews 2015; 9. Art No: CD004263.

- High (HIC), middle and low income countries (LWIC), hand washing prevention
  - Reduced about 1/3 of episodes of diarrhea
    - HIC
      - RR 0.70; 95% CI 0.58 to 0.85 (9 trials, 4664 participants)
    - LMIC
      - RR 0.66; 95% CI 0.43 to 0.99 (2 trials, 45380 participants)
- Behavior change
  - HIC
    - ↑ hand washing
  - LWIC
    - ↑ use of soap in hand washing
- The benefit on preventing diarrhea was greater when free soap was provided together with education about hand washing, vs hand washing education without free soap
  - Free soap
    - RR 0.66; 95% CI 0.56 to 0.78 (6 trials, 11422 participants)
  - No free soap
    - RR 0.84; 95% CI 0.67 vs 1.05 (2 trials, 3304 participants)
- Hand washing promotion in hospital among high-risk population ↓ mean episodes of diarrhea
  - MD 1.68; 95% CI 1.93 to 1.43 (1 trial, 148 participants)

Bottom Lines:

- The promotion of hand washing and the provision of free soap reduces episodes of acute diarrhea of about 30% in high, medium and low income countries, in hospital as well as in schools and in day care centres.



## H. pylori

- Helicobacter pylori eradication for the prevention of gastric neoplasia
  - "...searching for and eradicating H. pylori reduces the incidence of gastric cancer in healthy asymptomatic infected Asian individuals." (6 RCTs)
    - Preventing ↓ development of subsequent gastric cancer
      - RR 0.66, 95% CI 0.46 to 0.95; 6 trials, 6497 participants
    - Uncertain evidence for H. pylori eradication to ↓ mortality rate from gastric cancer

Ford AC, et al. Cochrane Library. Cochrane Database of Systemic Reviews 2015; 7. Art No: CD005582.

- Eradication therapy for peptic ulcer disease in H. pylori-positive people

Most gastric ulcer or duodenal ulcers are caused by H. pylori infection or by use of NSAIDs.  
Most DU/GU heal with 4-12 wk treatment with PPI.

- In persons with DU caused by H. pylori infection, with PPI plus 1-2 wk treatment H. pylori eradication therapy is superior to use of just PPIs or other ulcer healing drugs (UHDs), or to no treatment
  - RR of DU persisting
    - 0.66, 95% CI 0.58 to 0.76 (3 trials, 3910 participants)
- In persons with GU and H. pylori infection, the differences were imprecise between H. pylori eradication therapy and only UHDs
  - RR 1.23, 95% CI 0.90 to 1.68 (15 trials, 1974 participants)
- In preventing DU recurrence, the differences were imprecise between maintenance therapy with UHD
  - RR of DU recurrence 0.73, 95%CI 0.42 to 1.25 (4 trials, 319 participants)

### Take Home Message

- Treat H. pylori associated DU and GU rather than just using an ulcer healing drug such as PPI in order to better heal DU and the better prevent recurrence of GU.

Ford AC, et al. Cochrane Library. Cochrane Database of Systemic Reviews 2016; 4. Art.No: CD003846. ([www.cochranelibrary.com](http://www.cochranelibrary.com))



## Crohn Disease

### ➤ Induction of remission

Lim WC, et al. Cochrane Library. Cochrane Database of Systemic Reviews 2016; 7. Art No: CD008870.

- Aminosalicylates
    - Sulfasalazine
      - Non-significant trend over placebo at 17-18 wk, mostly in Crohn colitis 45% vs 29%
        - RR 1.38; 95% CI 1.00 to 1.89
      - Less effective than corticosteroids or corticosteroids plus sulfasalazine
        - RR 0.43; 95% CI 0.22 to 0.82
      - No difference in serious adverse or withdrawal, vs corticosteroids
    - Olsalazine
      - Less effective than placebo
        - RR 0.36; 95% CI 0.18 to 0.71
    - Mesalamine
      - 1-2 g/d
        - Not superior to placebo at 6 wk, 23% vs 15%
          - RR = 1.46; 95% CI 0.89 to 2.40
        - No difference in adverse events
          - RR 1.33; 95% CI 0.91 to 1.96
      - 4 g/d
        - Not superior to placebo
        - Inferior to budesonide
          - RR 0.56; 95% CI 0.40 to 0.78
        - No significant difference vs placebo or corticosteroids including budesonide
          - RR 2.02, 95% CI 0.75 to 5.45
          - RR 1.04, 95% CI 0.79 to 1.36; and
          - RR 0.89; 95% CI 0.76 to 1.05
- Bottom Lines
    - Sulfasalazine or mesalamine inferior to corticosteroids (including budesonide) in the induction of remission
    - Sulfasalazine or mesalamine have limited use in the induction of remission in persons with active Crohn disease



- Budesonide

- Superior to placebo at 8 wk
  - 47% vs 22%
    - RR 1.93; 95% CI 1.37 to 2.73
- Inferior to conventional corticosteroids
  - 52% vs 61%
    - RR 0.85%, 95% CI 0.75 to 0.97
  - Including in severe Crohn disease or more extensive colonic involvement
    - RR 0.52; 95% CI 0.75 to 0.97
  - Fewer adverse events
    - RR 0.64; 95% CI 0.54 to 0.76
- Similar to mesalamine
  - 69% vs 62%
    - RR 1.12; 95% CI 0.95 to 1.32
    - RR for abnormal ACTH test 0.65; 95% CI 0.55 to 0.48

- Bottom Lines
  - Conventional corticosteroids are superior to budesonide and to mesalamine for the induction of remission of Crohn disease but with fewer corticosteroid-associated adverse effects.

- Azathioprine (AZA) and 6-mercaptopurine (6-MP)

Chande N, et al. Cochrane Library. Cochrane Database of Systemic Reviews 2016; 10. Art No: CD000545.

- AZA / 6-MP vs placebo
  - No significant difference vs placebo
    - In achieving remission 48% vs 37%
      - RR 1.23; 95% CI 0.97 to 1.55)
    - In achieving clinical improvement or remission 48% to 36%
      - RR 1.26; 9% CI 0.98 to 1.62)
  - Significantly superior reduction of prednisolone dose to < 10 mg/d 64% vs 46%
    - RR 1.34; 95% CI 1.02 to 1.77)
  - No difference in withdrawal due to adverse events, or serious adverse events 10% vs 5%
    - RR 1.70; 95% CI 0.94 to 3.08)
  - But serious adverse events more common 14% vs 4%
    - RR 2.57; 95% CI 0.92 to 7.13)
- AZA / 6-MP vs methotrexate or sulfasalazine / aminosalicylate
  - No better in inducing steroid free clinical remission
    - RR 1.13; 95% CI 0.35 to 1.49, and
    - RR 1.24; 95% CI 0.80 to 1.91



- AZA vs infliximab
  - Inferior for steroid-free clinical remission 30% vs 44%
    - RR 0.68; 95% CI 0.51 to 0.90
  - Superior to infliximab alone when AZA combined with infliximab 60% vs 48%
    - RR 1.23; 95% CI 1.02 to 1.47
- AZA / 6-MP vs other drugs in withdrawals due to adverse events
  - Methotrexate
    - RR 0.78; 95% CI 0.23 to 2.71
  - Aminosalicylate / sulfasalazine
    - RR 0.98; 95% CI 0.38 to 2.54
  - Infliximab
    - RR 1.47; 95% CI 0.96 to 2.23

Bottom Lines:

Azathioprine (AZA) or 6-mercaptopurine (6-MP)

- Inferior to infliximab and no better than methotrexate, sulfasalazine / aminosalicylates or placebo for inducing steroid-free remission of active Crohn disease
  - Adding AZA / 6-MP to infliximab was superior to infliximab monotherapy
- Adverse events leading to study withdrawal was no different than placebo sulfasalazines, aminosalicylates or methotrexate or infliximab
  - Superior to placebo in corticosteroid-sparing effect (reducing prednisone dose < 10 mg/d)

▪ Methotrexate (MTX)

McDonald JWD, et al. Cochrane Library. Cochrane Database of Systemic Reviews 2014; 8. Art No: CD003459.

- Low dose (15 mg) oral
  - No placebo 33% vs 11%
    - RR 3.00; 95% CI 0.68 to 13.31
  - No 6-MP 62% vs 59%
    - RR 1.14; 95% CI 0.72 to 1.82
  - No 5-ASA 120% vs 86%
    - RR 0.23; 95% CI 0.08 to 0.67
- Higher dose IV / PO MTX plus AZA 44% vs 37%
  - RR 1.20; 95% CI 0.63 to 2.29
- High dose IM MTX vs placebo
  - Failure to enter remission 61% vs 81%
    - RR 0.75; 95% CI 0.61 to 0.93



- MTX plus infliximab vs infliximab monotherapy
  - No difference in failure to enter remission
    - IV / PO MTX 45% 62%
      - RR 0.73; 95% CI 0.31 to 1.69
    - SC MTX 24% vs 22% (
      - RR 1.07; 95% CI 0.57 to 2.03)
  - More common adverse events 17% vs 2%
    - RR 8.00; 95% CI 1.09 to 58.51)
- MTX vs AZA more adverse events 63% vs 26%
  - RR 2.42; 95% CI 1.21 to 4.89

Bottom Lines:

- High dose IM MTX is superior to placebo in the induction of remission and withdrawal of steroids
  - This benefit was accompanied with more adverse events than placebo or using azathioprine
- Adding MTX to infliximab was not superior to infliximab monotherapy

❖ Low dose naloxone (LDN)

Segal D, et al. Cochrane Library. Cochrane Database of Systemic Reviews 2014; 2. Art No: CD0010410.

- LDN vs placebo
  - No significant difference in clinical remission at 12 wk, 30% vs 18%
    - RR 1.48; 95% CI 0.42 to 5.24
  - Significantly higher in a 70-point clinical response, 83% vs 38%
    - RR 2.22; 95% CI 1.14 to 4.32
  - Significant higher endoscopic response (CDEIS decline  $\geq 5$  from baseline) 61% vs 31%
    - RR 1.96; 95% CI 0.87 to 4.42
  - But, no difference in endoscopic remission (CDEIS  $< 3$ ) 22% vs 0%
    - RR 8.05; 95% CI 0.47 to 38.87
  - No significant difference in withdrawals due to adverse events

Bottom Lines:

- In adults with Crohn disease, low dose naloxone is superior to achieve
  - A modest (70-point clinical response), but not a larger response or clinical remission
  - An endoscopic response, but not an endoscopic remission

Abbreviation: CDEIS, Crohn disease endoscopic index of severity



- Glutamine (GLU)

Akobeng AK, et al. Cochrane Library. Cochrane Database of Systemic Reviews 2016; 2. Art No: CD007348.

- GLU enriched vs low-glutamine polymeric diet (LGLU)
  - No difference in clinical remission rates at 4 wks 44% vs 56%
    - RR 0.80; 95% CI 0.31 to 2.04
  - Increased risk of central catheter infections with positive blood culture
    - RR 7.00; 95% CI 0.40 to 12.24

Bottom Lines:

- There is no evidence to support the use of glutamine-enriched polymeric diet as therapy for Crohn disease.

- Ustekinumab (USTs monoclonal antibodies that target the p40 subunit of cytokine IL-12)

McDonald JK, et al. Cochrane Library. Cochrane Database of Systemic Reviews 2016; 11. Art No: CD007572.

- UST vs placebo
  - 6 wk failure to enter remission 84% vs 90%
    - RR 0.92; 95% CI 0.88 to 0.96
    - Optimal dose 6 mg/kg
  - Clinical improvement failure
    - 70-point decline in CDAI score
      - 55% vs 71%
        - RR 0.78; 95% CI 0.71 to 0.85
    - 100-point decline in CDAI score
      - 64% vs 78%
        - RR 0.82; 95% CI 0.77 to 0.88
  - No difference in serious adverse events 62% vs 64%
    - RR 0.97; 95% CI 0.90 to 1.04

Bottom Lines:

- Ustekinumab is superior to placebo for inducing clinical remission / improvement in persons with moderately to severely acute Crohn disease, with no increased risk of adverse events.



- Endoscopic scoring indices for evaluation of disease activity in Crohn disease

Khanna R, et al. Cochrane Library. Cochrane Database of Systemic Reviews 2016; 8. Art No: CD010642.

- Before using scoring systems to assess endoscopic disease activity in Crohn disease, the operating characteristics must be studied and validated for reliability, responsiveness and correlation with other areas such as clinical laboratory and histopathological activity.
  - The CDEIS not the SES-CD (simple endoscopic scale) are incompletely validated and their use in clinical or research setting cannot be recommended.

- Maintenance of medically-induced remission in Crohn disease

Akobeng AK, et al. Cochrane Library. Cochrane Database of Systemic Reviews 2016; 9. Art No: CD003715.

- Aminosalicylic acid (5-ASA)

- 5-ASA vs placebo
  - No significant difference at 12 mon 53% vs 54%
    - RR 0.98; 95% CI 0.91 to 1.07
  - No difference in adverse events, serious adverse events, or withdrawals due to adverse events (e.g., adverse events, 34% vs 33%)
    - RR 1.05; 95% CI 0.95 to 1.17)

Bottom Lines:

- 5-aminosalicylic acid is of no proven benefit for the 12 or 24 mon maintenance of medically induced remission in Crohn disease.

- Antibiotics / anti-tuberculosis therapy (ATbT)

Patton PH, et al. Cochrane Library. Cochrane Database of Systemic Reviews 2016; 7. Art No: CD000299.

- ATbT vs placebo
  - Reduced relapse rates at 9 mon to 2 yr 39% vs 67%
    - RR 0.58; 95% CI 0.45 to 0.75
  - Increased adverse events
    - RR 2.57; 95% CI 1.45 to 4.55
  - But no difference withdrawals due to adverse events 9% vs 7%
    - RR 1.29; 95% CI 0.60 to 2.77

Bottom Lines:

- “Anti-tuberculosis therapy may provide a benefit for the prevention of relapse in participants with Crohn disease in remission...”
- “...this result is very uncertain due to unclear study quality and small number of patients assessed.”





- Budesonide (BUD) 6 mg

Kaenzig ME, et al. Cochrane Library. Cochrane Database of Systemic Reviews 2014; 8. Art No: CD002913.

- BUD vs placebo
  - No different than placebo for maintenance of remission at 3, 6, or 12 mon
    - 3 mon 64% vs 52%
      - RR 1.25; 95% CI 1.00 to 1.58
    - 6 mon 61% vs 52%
      - RR 1.15; 95% CI 0.95 to 1.39
    - 12 mon 55% vs 44%
      - RR 1.13; 95% CI 0.94 to 1.35
- BUD vs weaning dose of prednisolone
  - No difference
    - RR 0.79; 95% CI 0.55 to 1.13
- BUD vs
  - Mesalamine at 12 mon
    - Superior to mesalamine
      - RR 2.51%; 95% CI 1.03 to 6.12
  - Azathioprine
    - No difference
      - RR 0.81; 95% CI 0.61 to 1.08
    - Shorter mean time to relapse
      - MD -58.00, 95% CI -96.68 to -19.32
      - (Note: 1 small study found budesonide (6-9 mg/d) inferior to azathioprine (2.0 – 2.5 mg/kg) AZA vs BUD 76% vs 46%, RR 1.65; 95% CI 1.13 to 2.42)
    - Slight benefit in CDAI scores at 6 and 12 mon
      - MD -24.30, 95% CI -46.31 to -2.29, and
      - MD -23.49; 95% CI -46.65 to -0.32, respectively
    - Shorter mean time to relapse
      - MD 59.93, 95% CI 19.02 to 100.84
    - No difference in adverse events (e.g., BUD 6 mg)
      - RR 1.51, 95% CI 0.90 to 2.52
    - But risk of abnormal adrenocorticosteroid stimulation tests (e.g., 6 mg)
      - RR 2.88; 95% CI 1.72 to 4.82

Bottom Lines:

- Budesonide is beneficial for only 3 mon to maintain a medically-induced remission in Crohn disease
- The benefit of budesonide is comparable to azathioprine and superior to mesalamine
- While the use of budesonide for maintenance of Crohn disease has no difference in clinical adverse events, the long-term use of budesonide is associated with ↑ risk of an abnormal adrenocortical stimulation test.



- Azathioprine (AZA) or 6-mercaptopurine (6-MP)

Chande N, et al. Cochrane Library. Cochrane Database of Systemic Reviews 2015; 10. Art No: CD000067.

- Medically Induced Remission
  - AZA vs placebo
    - No difference in maintenance 73% vs 62%
      - RR 1.19, 95% CI 1.05 to 1.34; NNT = 9
    - ↑ risk of adverse events, serious events, withdrawal due to serious events (e.g., serious events, RR 2.45; 95% CI 1.22 to 4.90)
  - Mesalamine
    - No difference 69% vs 67%
      - RR 1.09, 95% CI 0.88 to 1.34
    - ↑ risk of adverse events
      - RR 9.37; 95% CI 1.84 to 47.7
  - AZA vs budesonide
    - No difference
      - RR 0.81; 95% CI 0.61 to 1.08
    - Shorter mean time to release
      - MD -58.00, 95% CI -96.68 to -19.32

(Note: 1 small study found budesonide (6-9 mg/d) inferior to azathioprine (2.0 - 2.5 mg/kg) AZA vs BUD 76% vs 46%, RR 1.65; 95% CI 1.13 to 2.42)

      - Slight benefit in CDAI scores at 6 and 12 mon
        - MD -24.30, 95% CI -46.31 to -2.29, and
        - MD -23.49; 95% CI -46.65 to -0.32, respectively
      - Shorter mean time to relapse
        - MD 59.93, 95% CI 19.02 to 100.84
      - No difference in adverse events (e.g., BUD 6 mg)
        - RR 1.51, 95% CI 0.90 to 2.52
      - But risk of abnormal adrenocortical stimulation tests (e.g., 6 mg)
        - RR 2.88; 95% CI 1.72 to 4.82
  - AZA plus infliximab monotherapy 12 mon
    - No difference 81% vs 80%
      - RR 1.02; 95% CI 0.74 to 1.40
  - 6-MP vs methotrexate, 12 mon
    - No difference 50% vs 53%
      - RR 0.94; 95% CI 0.47 to 1.87)
  - Early AZA vs conventional AZA
    - No difference 67% vs 56%



Bottom Lines:

- Azathioprine / 6-MP has a statistically significant but clinically small (~10%) benefit over placebo for the maintenance of remission in Crohn disease.
- AZA / 6-MP
  - No difference from budesonide, mesalamine, methotrexate or infliximab for the maintenance of remission in Crohn disease, and yet has
  - ↑ risk of adverse events

Gordon M, et al. Cochrane Library. Cochrane Database of Systemic Reviews 2014; 8. Art No: CD010233.

▪ Surgically Induced Remission

- AZA / 6-MP vs placebo
  - ↓ clinical relapse 48% vs 63%
    - RR 0.74; 95% CI 0.19 to 0.83
  - ↓ endoscopic relapse 17% vs 42%
    - RR 0.40; 95% CI 0.19 to 0.83
- AZA / 6-MP vs 5-ASA
  - No difference in clinical relapse at 1-2 yr 63% vs 54%
    - RR 1.15; 95% CI 0.99 to 1.34
  - ↑ withdrawal from adverse events 20% vs 10%
    - RR 2.07; 95% CI 1.26 to 3.39
  - No difference in endoscopic relapse at 12 mon AZA and 5-ASA
    - RR 0.78; 95% CI 0.52 to 1.17
  - 6-MP vs 5-ASA, 24 mon 17% vs 48%
    - RR 0.36, 95% CI 0.18 to 0.72
- AZA vs infliximab
  - Uncertain results for
    - Clinical remission
      - RR 2.00, 95% CI 0.21 to 18.98
    - Endoscopy remission
      - RR 4.40, 95% CI 0.59 to 3.07
- Adalimumab vs AZA
  - ↓ clinical relapse 1-2 yr
    - RR 5.18; 95% CI 1.35 to 19.83)
  - ↓ endoscopic relapse
    - RR 10.35; 95% CI 1.50 to 71.32)

Bottom Lines:

- Azathioprine (AZA) and 6-mercaptopurine (6-MP) are superior to placebo to maintain surgically induced Crohn disease
- Adalimumab but not infliximab may be superior to AZA / 6-MP for the reduction of clinical and endoscopic relapse.
- The result between AZA and 5-ASA is uncertain.



▪ Methotrexate (MTX)

Patel V, et al. Cochrane Library. Cochrane Database of Systemic Reviews 2014; 8. Art No: CD006884.

- MTX vs placebo
  - Low dose oral 12.5 mg/wk for 3 wk
  - Not effective for maintenance of remission of Crohn disease
  - Superior to placebo 65% vs 39%
    - RR 1.67; 95% CI 1.05 to 2.67, number needed to prevent one relapse ± 4
- MTX po vs 5-ASA
  - No difference 77% vs 57%
    - RR 1.06; 95% CI 0.92 to 2.07
- MTX vs 5-ASA
  - No difference
    - RR 2.62; 95% CI 0.23 to 29.79
- MTX vs MTX plus infliximab, 36-48 wk
  - No difference 54% vs 53%
    - RR 1.02; 95% CI 0.76 to 1.38

Bottom Lines:

- IM but not oral methotrexate (MTX) is superior to placebo for the maintenance of Crohn disease
- Adding infliximab to MTX does not ↑ benefit of MTX, and vice versa (infliximab vs infliximab plus MTX)
- There is no benefit between MTX and 6-MP or 5-ASA for the maintenance of Crohn disease

▪ Omega-3 (n=3) fatty acid (fish oil)

Lev-Tzion R, et al. Cochrane Library. Cochrane Database of Systemic Reviews 2014; 2. Art No: CD006320.

- n-3 therapy
  - Very low quality studies; 12 mon + marginal benefit 39% vs 47%
    - RR 0.77; 95% CI 0.61 to 0.98
  - Superior quality studies (lower risk of publication, unknown risk of bias)
    - No benefit 37% vs 42%
      - RR 0.88; 95% CI 0.74 to 1.05

Bottom Lines:

- “Evidence from two large high quality studies suggests that omega-3 fatty acids [fish oil] are probably ineffective for maintenance of remission in Crohn disease.



## COLON

### Ulcerative Colitis

#### ➤ Induction of remission

##### ▪ Oral 5-aminosalicylic acid (5-ASA) and salazopyrine (SASP)

Wang Y, et al. Cochrane Library. Cochrane Database of Systemic Reviews 2016; 4. Art No: CD000543.

- 5-ASA vs placebo
  - Failure to enter clinical remission 71% vs 83%
    - RR 0.86; 95% CI 0.82 to 0.89
    - Dose response effect for 5-ASA
    - No difference in efficacy between 5-ASA and SASP 54% vs 58%
      - RR 0.90; 95% CI 0.77 to 1.04)
    - No difference between 5-ASA dosed OD vs tid / qid
      - Patient failing to enter clinical remission 45% vs 48%
        - RR 0.94; 95% CI 0.83 to 1.07)
    - No difference in incidence of adverse events
      - Patients failing to adhere to medication regimen 8% vs 6%
        - RR 1.36; 95% CI 0.64 to 2.86)
    - “There does not appear to be any difference in efficacy among the various 5-ASA formulations
- 5-ASA vs 5-ASA
- Not as well tolerated 29% vs 15%
  - RR 0.48; 95% CI 0.37 to 0.63

#### Bottom Lines:

- 5-ASA is superior to placebo for the induction of acute ulceration colitis (UC).
- 5-ASA is equivalent to 5-ASA, and the various formulations of 5-ASA are no different.
- While there is a dose-response trend for 5-ASA, a dose of 2.4 g/d is adequate for moderately severe UC.
- 5-ASA may be taken once day.

#### ❖ Oral budesonide – MMX (B-MMX)

Sherlock ME, et al. Cochrane Library. Cochrane Database of Systemic Reviews 2015; 12. Art No: CD007698.

- B-MMX 9 mg vs placebo
  - Superior for inducing clinical and endoscopic remission at 8 wk 15% vs 8%
  - Most effective in left-sided UC
    - RR 2.98; 95% CI 1.56 to 5.67
  - No difference in withdrawal adverse effects
    - RR 0.89; 95% CI 0.53 to 1.36



- B-MMX vs prednisolone
  - No difference in endoscopic remission
    - RR 0.75; 95% CI 0.23 to 2.42
  - No difference in glucocorticoid-related side-effect
- B-MMX vs mesalamine (5-ASA)
  - No difference in remission rate
    - RR 1.48; 95% CI 0.81 to 2.71
- Standard budesonide vs mesalamine (5-ASA)
  - Inferior remission rates
    - RR 0.72; 95% CI 0.57 to 0.91
- B-MMX vs mesalamine
  - No difference in B-MMX when given with or without 5-ASA
- B-MMX vs standard budesonide
  - No difference
    - RR 1.38; 95% CI 0.72 to 2.65

Bottom Lines:

- Oral budesonide-MMX (B-MMX) 9 mg is superior to placebo in the induction of remission UC, particularly in L-sided UC.
  - B-MMX is no more effect with construction therapy with 5-ASA
- While there is no difference between B-MMX and standard budesonide, and B-MMX is no different than 5-ASA, standard budesonide is inferior to 5-ASA.
- B-MMX is no difference than prednisolone in activity endoscopic remission.

▪ Vedolizumab (VEDO)

Bickston SJ, et al. Cochrane Library. Cochrane Database of Systemic Reviews 2014; 8. Art No: CD007271.

- VEDO vs placebo for 4-6 wk in UC patients who
  - Failed to achieve clinical remission 77% vs 92%
    - RR 0.86; 95% CI 0.80 to 0.91; 4 studies, 606 participants
  - Failure to have a clinical response 48% vs 72%
    - RR 0.68; 95% CI 0.59 to 0.78
  - Failure to achieve endoscopic remission 68% vs 81%
    - RR 0.82; 95% CI 0.75 to 0.91
  - Clinical relapse after 52 wk of therapy 54% vs 84%
    - RR 0.67; 95% CI 0.59 to 0.77; 1 study, 373 participants
- VEDO vs placebo 6 and 52 wk, IBDQ
  - NO difference in adverse events, or serious adverse events
    - RR 0.99; 95% CI 0.93 to 1.07, and
    - RR 1.01; 95% CI 0.72 to 1.42, respectively



- Maintenance therapy: vedolizumab vs placebo
  - 6 wk 37% vs 23%
    - RR 1.62; 95% CI 1.15 to 2.27
  - 52 wk 64% vs 38%
    - RR 1.62; 95% CI 1.15 to 2.27, also at 52 wk, using SF-36 scores
  - VEDO was superior to placebo
    - MD 3.40; 95% CI 1.56 to 5.24

- Etrolizumab (ETRO)

Rosenfold G, et al. Cochrane Library. Cochrane Database of Systemic Reviews 2015; 12. Art No: CD011661.

- ETRO vs placebo, moderate to severe UC who failed conventional therapy
  - wk 6
    - Significant in reaching remission
    - Wk 6 91% vs 95%
      - RR 0.96; 95% CI 0.87 to 1.06; no dose response effect
  - wk 10
    - Significant difference to fail to enter remission 85% vs 100%
      - RR 0.86; 95% CI 0.77 to 0.95, do response present
    - Adverse effects less with Etro 56% vs 79%
      - RR 0.71 CI 0.55 to 0.91

Bottom Lines:

- In persons with moderate to severe ulcerative colitis, etrolizumab for 10 but not 6 wk may be useful salvage therapy for persons who have failed conventional therapy.

### Biologicals and Health-related quality of life

Rosenfold G, et al. Cochrane Library. Cochrane Database of Systemic Reviews 2015; 12. Art No: CD011661.

- The outcomes of biological trials for therapy in UC includes clinical, laboratory and endoscopic outcomes
- The health related quality of life (IBDQ) is reduced in persons with ulcerative colitis (UC) and is improved to a clinical meaningful extent
  - Induction therapy
    - Infliximab vs placebo 69% vs 50%
      - RR 1.39; 95% CI 1.21 to 1.60
  - Maintenance therapy: vedolizumab vs placebo
    - 6 wk 37% vs 23%
      - RR 1.62; 95% CI 1.15 to 2.27
    - 52 wk 64% vs 38%
      - RR 1.62; 95% CI 1.15 to 2.27, also at 52 wk, using SF-36 scores
    - VEDO was superior to placebo
      - MD 3.40; 95% CI 1.56 to 5.24



- Type I interferon

Wang Y, et al. Cochrane Library. Cochrane Database of Systemic Reviews 2015; 9. Art No: CD006790

- IFN vs prednisolone enemas
  - No benefit for inducing remission or clinical improvement by 8 to 12 wk in persons with left-sided active colitis 36% vs 30%
    - RR 1.16; 95% CI 0.84 to 1.58
- IFN vs placebo
  - No benefit for clinical improvement by 8 to 12 wk 56% vs 48%
    - RR 1.16; 95% CI 0.96 to 1.40
  - More withdrawals due to adverse effects 7% vs 2%
    - RR 3.16; 95% CI 1.06 to 9.40

Bottom Lines:

- Interferon PO / PR are not effective to induce remission in UC, and the withdrawals due to adverse effects were greater than placebo.

- ❖ Unfractionated (UFH) and low molecular weight heparin (LMWH)

Chande N, et al. Cochrane Library. Cochrane Database of Systemic Reviews 2015; 8. Art No: CD006774.

- LMWH extended colon-released tablet vs placebo in outpatients with mild to moderate UC
  - Clinical (judged to be very low quality of evidence)
    - Remission
      - RR 1.39; 95% CI 1.09 vs 1.77
    - Response
      - RR 1.28; 95% CI 1.06 to 1.55
  - Endoscopic
    - Remission (no benefit)
    - Response
      - RR 1.21; 95% CI 1.00 to 1.47
  - Histological improvement
    - No benefit
- LMWH when added to standard therapy
  - No added benefit
- UFH vs corticosteroids
  - No benefit (high risk of bias)
- LMWH SC vs placebo
  - No benefit for clinical improvement or remission, endoscopic or histological improvement





Bottom Lines:

- Low molecular weight heparin taken as extended colon-release tablets in outpatients with mild to moderate activity of UC has low quality evidence for clinical of UC has low quality evidence for clinical and endoscopic improvement.
- Heparin is used in selected patients with active UC to prevent thromboembolic disease, it is not certain that low molecular weight heparin will improve the UC activity, but that does not distract from the need to apply clinical practice guidelines to use UFH or LMWH for prophylaxis against potentially life-threatening thromboembolic disease.

▪ Helminth therapy (*Trichuris suis* ova [TSO])

Gary SK, et al. Cochrane Library. Cochrane Database of Systemic Reviews 2014; 1. Art No: CD009400.

- TSO vs placebo for 12 wk in UC (one small study of low quality due to serious imprecision)
  - Remission 10% vs 4%
    - RR 2.40; 95% CI 0.27 to 21.63
  - Clinical improvement 43% vs 17%
    - RR 2.60; 95% CI 0.97 to 6.95
  - Mean UCDAI lower
    - MD -1.40; 95% CI -1.75 to -1.05
  - Adverse effects 3% vs 12%
    - RR 0.27; 95% CI 0.03 to 2.40
- TSO vs placebo in CD
  - No clinical assessment

Bottom Lines:

- Limited and low quality data does not support a recommendation for worm therapy in UC or CD.



## Histological Scoring Indices in Ulcerative Colitis

Mosli MH, et al. Cochrane Library. Cochrane Database of Systemic Reviews 2017; 5. Art No: CD011256.

- “None of the available histological scoring indices have been fully validated”

### Bottom Lines:

- Azathioprine superior to placebo and methotrexate, but inferior to sulfasalazine or to mesalamine for maintenance of UC.
- The authors suggest that “azathioprine or 6-mercaptopurine may be effective as maintenance therapy for patients who have failed or cannot tolerate mesalamine or sulfasalazine and for patients who require repeated courses of steroids.
  - The statement is supported by indirect data and not direct comparison in RCTS

### ➤ Maintenance of remission

Timmer D, et al. Cochrane Library. Cochrane Database of Systemic Reviews 2016; 5. Art No: CD000478.

- Azathioprine (AZA) and 6-mercaptopurine (6-MP) (failure to maintain remission)
  - AZA vs placebo
    - Superior to placebo for 44% vs 65%
      - RR 0.68; 95% CI 0.54 to 0.86
  - AZA vs sulfasalazine
    - Failed to maintain remission 58% vs 38%
      - RR 1.52; 95% CI 0.66 to 3.50
  - 6-MP vs mesalamine
    - Failed to maintain remission 50% to 100%
      - RR 0.53; 95% CI 0.31 to 0.90
  - 6-MP vs methotrexate
    - Maintain (remission) 50% vs 92%
      - RR 0.55; 95% CI 0.31 to 0.90

### ▪ Methotrexate (MTX)

Wang Y, et al. Cochrane Library. Cochrane Database of Systemic Reviews 2015; 8. Art No: CD007560.

- MTX (12.5 mg/wk PO) vs placebo, 9 mon
  - No difference in maintaining remission at 9 mon 36% vs 54%
    - RR 0.64; 95% CI 0.28 to 1.45
- MTX plus sulfasalazine vs sulfasalazine monotherapy
  - No difference at 12 mon 100% vs 75%
    - RR 1.32; 95% CI 0.94 to 0.86



- MTX vs 6-MP
  - No significant difference at 76 wk (quality of evidence was low due to high risk of bias and very sparse data)
    - 14% vs 64%
      - RR 0.22; 95% CI 0.03 to 1.45
- MTX vs 5-ASA 14% vs 0%
  - RR 1.13, 95% CI 0.06 to 20.71

Bottom Lines:

- Oral methotrexate was not superior to placebo, sulfasalazine, 6-mercaptopurine on 5-amino salicylic acid for maintenance of remission in ulcerative colitis.

- Tolerability Cyclooxygenase 2 inhibitor for rheumatological manifestation of inflammatory bowel disease

Wang Y, et al. Cochrane Library. Cochrane Database of Systemic Reviews 2014; 10. Art No: CD007744.

- Etoricoxib vs placebo
  - No ↑ exacerbations of IBD after 12 wk 17% vs 19%
    - RR 0.88; 95% CI 0.45 to 1.69
- Celecoxib vs placebo
  - No ↑ exacerbations of IBD after 2 wk 4% vs 6%
    - RR 0.70; 95% CI 0.23 to 2.14
  - No ↑ adverse events 21% vs 17% ( $P > 0.20$ )

Bottom Lines:

- Celecoxib and etoricoxib did not worsen IBD symptoms in two small studies with short follow-up durations.

- Treatment and Prevention of pouchitis after ileal pouch-anal anastomosis (IPAA) for chronic ulcerative colitis

Singh S, et al. Cochrane Library. Cochrane Database of Systemic Reviews 2015; 11. Art No: CD001176.

- Treatment
  - Acute pouchitis
    - Ciprofloxacin vs metronidazole for 2 wk 100% vs 33% remission very low quality due to high risk of bias
    - No difference but very low quality
      - Rifaximin vs placebo
      - Lactobacillus GG vs placebo



- Chronic pouchitis (maintenance of remission)
  - VSL#3 vs placebo 85% vs 3% maintenance of remission at 9 - 12 mon
  - RR 20.24; 95% CI 4.28 vs 95.81
- Prevention
  - VSL#3 vs placebo 90% vs 60% at 12 mon
  - RR 1.50; 95% CI 1.02 - 2.21
  - Low quality evidence due to very sparse data

Bottom Lines:

- Only low quality evidence supports that use of
  - Ciprofloxacin vs metronidazole for acute pouchitis
  - VSL#3 for maintenance of remission and for prevention of pouchitis

### Colorectal Cancer and Surgery

▪ Chromoscopy versus conventional endoscopy for the detection of polyps of the colorectum  
Brown SR, et al. Cochrane Library. Cochrane Database of Systemic Reviews 2016; 4. Art No: CD006439.

- Seven trials involving 2727 participants favoured chromoscopy for polyp detection
  - More people with at least one neoplastic lesion
    - RR 1.53; 95% CI 1.31 to 1.79; 7 trials 2727 participants
  - $\geq 1$  diminutive neoplastic lesion
    - OR 1.51; 95% CI 1.19; 4 trials, 1757 participants
  - More people with  $\geq 3$  neoplastic lesions (high-definition colonoscopy)
    - OR 4.63; 95% CI 1.99 to 10.80; 2 trials, 519 participants

Bottom Lines:

- Chromoscopy enhances detection of neoplasia in the colon and rectum

▪ Water Infusion versus air insufflation for colonoscopy

Hafner S, et al. Cochrane Library. Cochrane Database of Systemic Reviews 2015; 5. Art No: CD009863.

- Cecal intubation rate was not increased by water infusion compared with air insufflation, but water infusion was associated with
  - $\uparrow$  adenoma detection
    - $\uparrow$  adenoma detection rate
    - $\uparrow$  adenomas detected per procedure
  - $\downarrow$  procedure-related abdominal pain



## Colorectal Cancer (CRC)

### ➤ Non-metastatic CRC

#### ▪ Antimicrobial Prophylaxis

Nelson RL, et al. Cochrane Library. Cochrane Database of Systemic Reviews 2014; 5. Art No: CD001181.

- Prophylactic antibiotics are superior to placebo / no treatment in the prevention of post colorectal surgery wound infections
  - RR 0.34; 95% CI 0.28 to 0.41 (reduction of risk from 39% to 13%)
  - Multiple dosing and longer duration of antibiotics may be superior
- Antibiotic regimen
  - Additional aerobic as well as anaerobic coverage reduced rates of surgical wound infection
    - RR 0.44; 95% CI 0.29 to 0.68 (aerobic coverage), and
    - RR 0.47; 95% CI 0.31 to 0.71 (anaerobic coverage)
  - Combined oral plus IV antibiotic prophylaxis versus only oral antibiotics reduced rates surgical wound infection compared to only IV antibiotics
    - RR 0.56; 95% CI 0.43 to 0.74
  - Oral antibiotic prophylaxis versus only IV antibiotics
    - RR 0.56; 95% CI 0.40 to 0.76
  - There was no difference in rate of surgical wound infection when giving prophylactic antibiotics before or after surgery
    - RR 0.67; 95% CI 0.21 to 2.15
  - Established gold-standard regimens recommended in major guidelines were no less effective than any other antibiotic choice.”

#### Bottom Lines:

- When the colon is empty before surgery, antibiotics covering aerobic and anaerobic bacteria given orally, intravenously, or orally plus intravenously before elective colorectal therapy reduce the risk of surgical wound infection by as much as 75%.

#### ▪ Laparoscopic (LTME) versus open total mesorectal excision (OTME) for rectal cancer

Vennex S, et al. Cochrane Library. Cochrane Database of Systemic Reviews 2014; 4. Art No: CD005200.

#### ❖ Laparoscopic mesorectal excision and comparable to open total mesorectal excision (OTME) for rectal cancer

- Short term
  - ↓ length of hospital stay 2 days (95% CI -3.22 to -1.10)
  - ↓ time to first defecation
    - -0.86 days; 95% CI -1.17 to -0.54)
  - ↓ wound infections
    - OR 0.68; 95% CI 0.50 to 0.93)



- ↓ bleeding complications
  - OR 0.30; 95% CI 0.10 to 0.93
- Similar 30 day morbidity
  - OR 0.94; 95% CI 0.8 to 1.1
- Long-term (no difference between groups)
  - 5-yr disease free
    - OR 1.02; 95% CI 0.76 to 1.38)
  - ↓
  - Local recurrence
    - OR 0.89; 95% CI 0.57 to 1.39
  - Overall survival
    - OR 1.15; 95% CI 0.87 to 1.52
  - Number of resected lymph nodes
  - Surgical margins

Bottom Lines:

- Laparoscopic total mesorectal excision is superior to open total mesorectal excision for colorectal cancer, with no adverse effects on long-term outcome, as compared with open resection.

- Combination chemotherapy versus single-agent chemotherapy during preoperative chemoradiation for resectable rectal cancer

Resende HM, et al. Cochrane Library. Cochrane Database of Systemic Reviews 2015; 10. Art No: CD008531.

- Resectable rectal cancer, four RCTs with 3875 participants, with preoperative radiotherapy plus either capecitabine or 5-fluorouracil (fluoropyrimidine agent), or with capecitabine or 5-fluorouracil plus oxaliplatin.
- Pathological complete response after preoperative was superior with the combination of oxaliplatin plus a fluoropyrimidine versus a fluoropyrimidine alone
  - OR 1.23; 95% CI 1.04 to 1.46
  - However, the early toxicity was higher with the combination than in the monotherapy group
    - OR 2.07; 95% CI 1.31 to 3.27
    - The lower toxicity in the monotherapy group was associated with better compliance to radiotherapy than did the combination group
  - OR 0.32; 95% CI 0.14 to 0.75

Bottom Lines:

- Oxaliplatin plus a fluoropyrimidine with radiotherapy before resection of rectal cancer provided greater local control of the rectal cancer, but the regimen was more toxic than with fluoropyrimidine agent alone (capecitabine or 5-fluorouracil).



▪ Follow-up strategies for patients treated for non-metastatic colorectal cancer

Jeffery M, et al. Cochrane Library. Cochrane Database of Systemic Reviews 2016; 11. Art No: CD002200.

- Patients with colorectal cancer (CRC) are often followed for several years (intensive follow-up) after their curative surgery, adjuvant therapy, or both
  - Another approach is to follow the patient less frequently, depending upon the recurrence of symptoms
- Intensive follow-up compared with interval (symptomatic) recurrences was not associated with improved
  - Overall survival
  - CRC-specific survival
  - Relapse-free survival
  - Relapse-free survival
  - Better quality of life
  - Harm from colonoscopies
  - Intensive follow-up was associated with
    - More salvage surgery with curative intent
      - RR 1.98; 95% CI 1.53 to 2.56
    - Less frequent interval (symptomatic recurrence)
      - RR 0.59; 95% CI 0.41 to 2.86)

Note that those who had intensive follow-up with curative intent had salvage surgery, their overall and CRC-specific survival was not improved.

Bottom Lines:

- There is not an improved overall or cancer specific survival or better quality of life from a program of intense follow-up as compared to those patients seen at intervals when their symptoms had recurred.

- ❖ Recurrent colorectal cancer and blood carcino-embryogenic antigen (CEA) levels for detecting recurrence of colorectal cancer (CRC) is influenced by the cut-off concentration which when reached will trigger further diagnostic investigation for possible CRC recurrence.

Nicholson BD, et al. Cochrane Library. Cochrane Database of Systemic Reviews 2015; 12. Art No: CD011134.

| Cut-off for Upper Limit of Normal for Blood CEA, µg/L | Performance Characteristics |             |
|-------------------------------------------------------|-----------------------------|-------------|
|                                                       | Sensitivity                 | Specificity |
| 2.5                                                   | 82%                         | 80%         |
| 5                                                     | 71%                         | 88%         |
| 10                                                    | 68%                         | 97%         |

- CEA measurement should be set a cut-off no more than 10 µg/L, and must be used with another diagnostic modality, such as surveillance colonoscopy, to avoid recurrences.



Bottom Lines:

- “There is a lack of evidence from existing RCTs to suggest that increased dietary fiber intake will reduce the recurrence of adenomatous polyps within a two to eight year period.”
  - Keep focused on emerging data which continues to support the role of statins, ASA, NSAIDs and Coxibs to reduce the incidence of index or recurrence colonic adenomatous polyps.

## Metastatic Colorectal Cancer

- Second line systemic therapy
  - Classes of anti-cancer regimens were analyzed in persons with CRC that progressed, recurred or did not respond to first time systemic chemotherapy.
    - Targeted agents may be combined with conventional drugs to achieve superior results
  - Irinotecan vs best supportive care
    - More effective
      - HR (or overall survival)
        - 0.58; 95% CI 0.43 to 0.80
  - Irinotecan or 5-fluorouracil (5-FU) plus leucovorin plus oxaliplatin; FOL FOX versus 5-FU monotherapy
    - More effective
      - Overall survival
        - HR 0.60; 95% CI 0.51 to 0.94
      - Progression-free survival
        - HR 0.59; 95% CI 0.49 to 0.73
  - Irinotecan-based combinations versus irinotecan monotherapy
    - More effective
      - Progression-free survival
        - HR 0.68; 95% CI 0.60 to 0.76
  - Targeted agents plus conventional therapy vs conventional therapy alone
    - Superior outcome) overall survival
      - HR 0.84; 95% CI 0.77 to 0.91
  - Bevacizumab plus conventional therapy
    - Superior outcome (progression free survival)
      - HR 0.67; 95% CI 0.60 to 0.75
  - Tumor response rates usually
    - Parallel survival rates
    - Have greater toxicity
    - Exception
      - Bevacizumab has higher tumour response rates without necessary greater toxicity procedures
  - The toxicity of fluoropyrimidines have lower toxicity but unchanged efficacy if given by mouth





Bottom Lines:

- Systemic therapy [such as irinotecan] offers a survival benefit to people with metastatic CRC who do not respond to first-line treatment...
  - Especially when targeted agents are combined with conventional chemotherapeutic drugs.”

- Epidermal growth factor receptor (EGFR) inhibitors for metastatic colorectal cancer

Chan DLH, et al. Cochrane Library. Cochrane Database of Systemic Reviews 2017; 6. Art No: CD004047.

Bottom Lines:

- Adding EGFR MAb to standard therapy in patients with metastatic CRC who were either KRas exon 2 wild-type or Ras wild type improves progression-free survival, overall survival and response to chemotherapy
- EGFR MAb (EGFR monoclonal antibodies) vs standard chemotherapy in persons with metastatic colorectal cancer (CRC) of the KRas exon 2 wild-type improves
  - Progression-free survival
    - HR 0.70; 95% CI 0.60 to 0.82
  - Overall survival
    - HR 0.88; 95% CI 0.80 to 0.98
  - Response rate to chemotherapy
    - OR 2.41; 95% CI 1.70 to 3.41
  - Adverse effects increased but no increased neutropenia
  - EGFR MAb plus bevacizumab plus chemotherapy did not improve these outcomes
- EGFR MAb is standard chemotherapy in persons with Ras wild-type CRC (no mutations in KRas or NRas) improves
  - Progression-free survival
    - HR 0.60; 95% CI 0.48 to 0.75
  - Overall survival
    - HR 0.77; 95% CI 0.67 to 0.88
  - Response rate
    - OR 4.28; 95% CI 2.61 to 7.03
- EGFR MAb vs bevacizumab
  - No difference in
    - Progression-free survival
      - HR 1.02; 95% CI 0.93 to 1.12
    - Overall survival
      - HR 0.84; 95% CI 0.70 to 1.01
- EGFR TKI (EGFR tyrosine kinase inhibitors) did not improve these outcomes in molecularly unselected patients with metastatic CRC.



## Fecal Incontinence

- Sacral nerve stimulation (SNS) for fecal incontinence and constipation in adults

Thaha MA, et al. Cochrane Library. Cochrane Database of Systemic Reviews 2015; 8. Art No: CD004464.

- Fecal incontinence (defined as “involuntary passage of fecal material through the anal canal”)
  - SNS vs control group (optimal medical therapy) fewer episodes of fecal incontinence
    - 3 mon
      - MD -5.20; 95% CI -9.15 to 11.25
    - q 12 mon
      - MD -6.30; 95% CI -10.34 to -2.26
    - Adverse events included
      - Excessive tingling in vaginal area (9%)
      - Pain at implantation site of SNS (6%)
      - Seroma (2%)
  - SNS vs PTNS (percutaneous tibial nerve stimulation)
  - Preferred “PN” period of stimulation in cross-over studies (“on” vs “off”)
    - 19 persons preferred “on”, 5 preferred “off”
- Constipation
  - SNS did not improve constipation in persons with constipation

### Bottom Lines:

- Sacral nerve stimulation is superior to optimal medical therapy or the percutaneous tibial nerve stimulation to improve fecal incontinence with fecal incontinence.

- Plugs for containing fecal incontinence

Deutekon M, et al. Cochrane Library. Cochrane Database of Systemic Reviews 2015; 7. Art No: CD005086.

- Data is limited and incomplete.
- About 1/3 of persons with fecal incontinence cannot tolerate a plug.
- Plug loss was less, and satisfaction was greater with the use of polyurethane versus polyvinyl-alcohol plugs.



## Constipation

### ▪ In pregnancy

Rungsiprakarn P, et al. Cochrane Library. Cochrane Database of Systemic Reviews 2015; 9. Art No: CD011448.

- Fiber supplementation vs no intervention
  - ↑ stool frequency
    - MD 2.24 times per wk, 95% CI 0.96 to 3.52
  - Improved stool consistency
    - Hard stool ↓ 11% to 14%
    - Normal stool ↑ 5% to 10%
    - Loose stool ↑ 0% to 6%
- Stimulant laxatives (Senokot, Normax no longer used in pregnancy / breastfeeding) vs bulk-forming laxative
  - ↓ constipation
    - RR 1.59; 95% CI 1.21 to 2.09
  - ↑ discomfort
    - RR 2.33; 95% CI 1.15 to 4.73
  - Borderline difference in diarrhea
    - RR 4.50; 95% CI 1.01 to 20.09
  - No difference in woman's satisfaction
    - RR 1.06; 95% CI 0.77 to 1.46

#### Bottom Lines:

- In pregnancy stimulant laxatives are more effective in the improvement of constipation than one bulk-forming laxative or no intervention
  - Despite the improvement in symptoms, there is no difference in the woman's satisfaction when stimulant laxative are compared to bulk-forming agents.
- Stimulant laxatives are likely to increase the woman's diarrhea

### ▪ Palliative Care

Candy B, et al. Cochrane Library. Cochrane Database of Systemic Reviews 2015; 5. Art No: CD003448.

- There were 5 studies identified by the authors for the Cochrane Collaboration, and different laxative or combinations of laxatives were used, making it not possible to perform a meta-analysis for effectiveness or for adverse effects.
  - Studies have not yet reported on the use of oral or rectal polyethylene glycol
    - The authors of this Cochrane review advise against extrapolating finding from other population groups to those persons who reviews palliative care.



### ▪ Anti-psychotic-related Constipation

Every-Palmer S, et al. Cochrane Library. Cochrane Database of Systemic Reviews 2017; 1. Art No: CD011128.

- Mannitol vs rhubarb soda or phenothalein more effective in relieving constipation within 24 hr
  - RR 0.07; 95% CI 0.02 to 0.27
- Glycerol suppository vs traditional Chinese medicine (TCM tuina massage and acupuncture)
  - Less effective than TCM
    - Day 2
      - RR 2.88; 95% CI 1.89 to 4.39
    - Day 3
      - RR 4.80; 95% CI 1.96 to 11.74
- Acupuncture
  - Day 2
    - RR 3.50; 95% CI 2.18 to 5.62
  - Day 3
    - RR 8.0; 95% CI 2.54 to 25.16

#### Bottom Lines:

- The limited available studies are of very low quality and have a high risk of bias.
  - On the basis of the available data, mannitol may be effective for anti-psychotic constipation.
- The role of massage and acupuncture cannot be recommended until future studies are performed with modern Consort reporting prerequisites.

### ▪ Prevention of postpartum constipation

Turawa EB, et al. Cochrane Library. Cochrane Database of Systemic Reviews 2015; 9. Art No: CD011625.

- Laxative vs placebo for first postpartum bowel movement
  - More women having first bowel movement (BM) in first 24 hr
    - RR 2.90; 95% CI 2.24 to 3.75 (1 trial, 471 women)
  - Fewer women having their first BM by day 4
    - RR 0.36; 95% CI 0.21 to 0.61 (2 trials, 671 women)
  - More women having loose or watery stools
    - RR 26.96; 95% CI 3.81 to 191.03 (1 trial, 106 women)
  - No difference in number of enemas administered
    - RR 0.63; 95% CI 0.38 to 1.05 (1 trial 244 women)
  - Abdominal cramps
    - Could not be pooled in meta-analysis; inconsistent results
- Laxatives vs bleeding agent plus laxative (third degree perianal tears) (inconsistent data)
  - No difference in pain, straining
  - Time to first BM
  - More fecal incontinence with bulk plus laxative



Bottom Lines:

- “Result from trials were inconsistent and there is insufficient evidence to make general conclusions about the effectiveness and safety of laxatives.”

▪ Biofeedback

Woodward S, et al. Cochrane Library. Cochrane Database of Systemic Reviews 2014; 3. Art No: CD008486.

- In persons with chronic constipation +/-dysynergic defecation, electromyography (EMG) biofeedback vs diazepam po.
  - Manometry feedback improvement in conventional treatment 70% vs 23%
    - RR 3.00; 95% CI 1.51 to 5.98
    - Greater number of spontaneous bowel movements per wk at 3 mon 4.6 vs 28
      - MD 1.80; 95% CI 1.25 to 2.35
  - EMG feedback vs conventional therapy
    - Greater clinical improvement at 6 and 12 mon 80% vs 22%
      - RR 3.65; 95% CI 2.17 to 6.13
  - Surgery (partial division of puborectalis muscle and stapled transanal rectal resection [STARR]) vs biofeedback
    - Greater ↓↓ obstructed defecation score of  $\geq 50\%$  at 1 yr 82% vs 33%
      - RR 0.41; 95% CI 0.26 to 0.65)
  - Balloon sensory biofeedback vs partial division of puborectal muscle (not confirmed in second study)
    - ↓ constipation score in the surgical group 10.5 vs 16.1 (comparing biofeedback to surgery)
      - MD 5.60; 95% CI 4.67 to 6.53

Bottom Lines:

- Biofeedback may be superior to diazepam, sham feedback, and conventional therapy, but inferior to surgical therapy for the treatment of chronic complication.
  - However, the studies are of low quality and are subject to bias.

- Biofeedback vs injection of botulinum toxin-A
  - Uncertain results: small trial; low quality, high risk of bias



- Central neurological disease

- Parkinson disease

- Psyllium / isosmotic solution vs placebo
  - ↑ number of bowel movements per wk / ↑ success of bowel care routines
    - Psyllium
      - MD -2.2 BMs/per wk; 95% CI -3.3 to 1.4
    - Isosmotic macrogel electrolytic solution
      - MD 2.9 BMs/wk; 95% CI 1.48 to 4.32

- Spinal cord injury

- Neostigmine-glycopyrrolate vs placebo
  - ↑ in time to BM vs placebo
    - MD 23.3 min; 95% CI 4.68 to 41.92
- Polyethylene-glycol-based (PGB) vs hydrogenated vegetable oil based (HVB) suppositories
  - ↓ mean defecation period 20 mm vs 36 mm ( $P < 0.03$ )
  - ↓ mean total time for bowel care 43 mm vs 25 mm ( $P < 0.01$ )
- Abdominal muscle electrical stimulation vs no stimulation
  - ↓ mean time for bowel care
    - MD 29.3 min; 95% CI 7.35 to 51.25
- Transanal irrigation vs conventional bowel care
  - ↓ scores for constipation, neurogenic bowel dysfunction, fecal incontinence, time for bowel care; ↑ patient satisfaction
    - MD 27.4 min; 95% CI 7.96 to 46.84

- Stroke

- Abdominal massage vs no massage
  - ↑ number of BMs per wk at 6 but 12 mon
- Targeted education (one-off) vs routine care
  - ↑ number of BMs per wk (abstract only)

Bottom Lines:

- There is limited evidence to support supplementing routine bowel care in persons with central neurogenic diseases with psyllium, isosmotic electrolyte solution, anticholinesterase, anti-cholinesterase drug combination of neostigmine-glycopyrrolate, as well as abdominal massage, electrical stimulation transanal irrigation, drinking carbonated water and educational instruction.



## Lymphocytic Colitis

Chande N, et al. Cochrane Library. Cochrane Database of Systemic Reviews 2017; 7. Art No: CD006096.

- Budesonide (9 mg/d for 6-8 wk)
  - More effective than placebo for
    - Clinical response 88% vs 38%
      - RR 2.03; 95% CI 1.25 to 3.33 (2 studies, 57 participants)
    - Histological response 78% vs 33%
      - RR 2.44; 95% CI 1.13 to 5.28
- Mesalamine (2.4 g/day) vs mesalamine plus cholestyramine (4 g/d)
  - Mesalamine monotherapy gave a similar clinical response as the combined therapy 85% vs 86%
    - RR 0.99; 95% CI 0.77 to 1.28
- Beclometasone dipropionate (5 or 10 mg/d) vs mesalamine (2.4 g/d)
  - No difference in clinical remission
    - 8 wk 84% vs 86%
      - RR 0.97; 95% CI 0.75 to 1.24
    - 12 mon
      - RR 1.29; 95% CI 0.40 to 4.18
  - 8 wk remissions were not maintained at 12 mon

### Bottom Lines:

- Low quality evidence suggests that budesonide mesalamine +/- cholestyramine or beclometasone dipropionate may be effective in treating lymphocytic colitis
  - Long-term outcome data needed to establish if clinical remissions achieved after short term treatment are sustained long-term.
  - Larger comparative studies are required.

## Clostridium Difficile (C. difficile) Infection (CDI)-associated Diarrhea

- Antibiotics treatment, non-severe CDI
  - Vancomycin (VAN) vs metronidazole (MET)
    - Greater symptomatic cure 79% vs 72% (MET vs VAN)
      - RR 0.99; 95% CI 0.84 to 0.97
  - Fidaxomicin (FID) vs vancomycin
    - Greater symptomatic cure 71% vs 61%
      - RR 1.17; 95% CI 1.04 to 1.31
  - Teicoplanin (TEI) vs vancomycin
    - Greater symptomatic care 87% vs 73%
      - RR 1.21; 95% CI 1.00 to 1.46



Bottom Lines:

- In patients with mild-to-moderate *Clostridium difficile* infection, the appropriate relative potency of antibiotics to provide symptomatic cure is metronidazole < vancomycin < teicoplanin / fidaxomicin (is the most costly).

■ Probiotics for the prevention of CDI

Goldenberg JZ, et al. Cochrane Library. Cochrane Database of Systemic Reviews 2017; 12. Art No: CD006095.

- Probiotics vs no probiotics in persons with *C. difficile*-associated diarrhea (CDAD)
  - Overall ↓ risk of CDAD by 60%
    - RR 0.40; 95% CI 0.30 to 0.52; NNTB = 12 (31 trials, 8672 participants)
  - High risk patients for CDAD (> 5%)
    - ↓ risk by 70% (absolute risk 3.1% vs 11.6%)
      - RR 0.30; 95% CI 0.21 to 0.42 (13 trials, 2454 participants)
  - Low risk patients for CDAD (0% to 5%)
    - No benefit in decreasing CDAD

Bottom Lines:

- Persons with a greater than 5% baseline risk of developing *C. difficile*-associated diarrhea (CDAD) have a marked (70%) reduction in their risk of CDAD.

■ Enhanced Recovery Protocols for Major Upper Gastrointestinal Hepatic or Pancreatic Surgery

Bond-Smith G, et al. Cochrane Library. Cochrane Database of Systemic Reviews 2016; 2. Art No: CD011382.

Bottom Lines:

- In persons with low anaesthetic and high performance states who are having major upper gastrointestinal, hepatic or pancreatic surgery, non-randomized clinical trials (non RCTs) suggest multiple benefits such as short-term mortality, adverse events, health-related quality of life, length of hospital stay and costs, hospital readmission.
  - However, the validity of these suggestions must be challenged because the studies were based mostly on low quality evidence and high risk of bias.





## Diverticular Disease

- Mesalamine versus no mesalamine to prevent recurrence of colonic diverticulitis

Carter F, et al. Cochrane Library. Cochrane Database of Systemic Reviews 2017; 10. Art No: CD009839.

- No difference
  - RR 0.98; 95% CI 0.91 to 1.06 (7 trials, 1805 participants)

### Bottom Lines:

- Evidence does not support the use of mesalamine to reduce the risk of recurrent diverticulitis.

## APPENDIX

- Acute lower abdominal pain in young women

Gaitan HG, et al. Cochrane Library. Cochrane Database of Systemic Reviews 2014; 5. Art No: CD009683.

- In women of child-bearing age, acute lower abdominal pain may have numerous causes, e.g.,
  - Gynecological / obstetrical ovulation / menstruation
    - Complications of pregnancy
    - Pelvic inflammatory disease
  - Non gynecological / obstetrical conditions e.g., acute appendicitis
- Laparoscopy versus open appendectomy
  - ↑ rate of specific diagnosis
    - OR 4.10; 95% CI 2.50 to 6.71 (7 RCTs, 561 participants)
    - No difference rates of adverse events
      - OR 0.46; 95% CI 0.19 to 1.10; 8 RCTs, 623 participants)
    - ↓ rate of removal of a normal appendix (i.e., incorrect diagnosis)
      - OR 0.13; 95% CI 0.007 to 0.24 (7 RCTs, 475 participants)
- Laparoscopy versus “wait and see” approach
- ↑ rate of specific diagnosis
  - OR 6.07; 95% CI 1.85 to 29.88 (4 RCTs, 395 participants)
- No difference in rate of adverse effects
  - OR 0.87; 95% CI 0.45 to 1.67

### Bottom Lines:

- In young women with acute lower abdominal pain in whom acute appendicitis is suspected, performing either laparoscopy rather than a “wait and see” approach or open appendicitis increases the rate of specific diagnosis, has no difference in rate of adverse events, and may reduce the rate of removal of a normal appendix.



❖ Timing of appendectomy for appendiceal phlegmon

Cheng Y, et al. Cochrane Library. Cochrane Database of Systemic Reviews 2017; 6. Art No: CD011670.

- Early versus delayed open appendectomy for appendiceal phlegmon
  - Insufficient evidence to determine difference in
    - Overall morbidity
      - RR 13.00; 95% CI 0.78 to 216.39
    - Development of wound infection
      - RR 9.00; 95% CI 0.52 to 156.91
    - Development of fecal fistula
      - RR 3.00; 95% CI 0.13 to 69.52
    - Length of hospital stay / times away from normal activities
      - MD 6.70 d; 95% CI 2.76 to 10.64, and
      - MD 5.00 d; 95% CI 1.52 to 8.48 d, respectively

Bottom Lines:

- Data is unclear as to the optimal timing for appendectomy in the patient with acute appendicitis.

## LIVER

### Non-Alcohol Related Fatty Liver Disease (NAFLD)

Lombarde R, et al. Cochrane Library. Cochrane Database of Systemic Reviews 2017; 3. Art No: CD011640.

❖ Pharmacological Treatment Adverse Events

Bottom Lines:

- Anti-oxidants, bile acids and thiazolidinediones versus no intervention in persons with NAFLD or NASH, whether diabetic or non-diabetic use not associated with mortality and there was no ↑ risk of serious adverse events.
  - The benefit of these drugs in persons with NAFLD / NASH is reviewed elsewhere, but these drugs do not cause any mucosal risk of severe adverse events or of mortality (77 trials, 6287 participants)

### Hereditary Hemochromatosis

Buzzett E, et al. Cochrane Library. Cochrane Database of Systemic Reviews 2017; 3. Art No: CD011647.

- "...there is no evidence from randomized clinical trials that blood letting in any form is beneficial in people with hereditary hemochromatosis."
- Comparing erythrocytapheresis (removal of RBCs) versus phlebotomy (removal of RBCs plus plasma), there were no differences in short term mortality, serious adverse events, or short term quality of life (EQ-VAS).



Bottom Lines:

- Phlebotomy is the standard of care for persons with iron overload due to hereditary hemochromatosis.
- Removal of just the red blood cells does not appear to cause any difference in mortality, morbidity or quality of life
  - The clinical efficacy of erythrocytapheresis remain to be demonstrated through RCTs.

### Primary Biliary Cholangitis (PBC)

Saffioti F, et al. Cochrane Library. Cochrane Database of Systemic Reviews 2017; 3. Art No: CD011648.

- “Base on very low quality evidence, there is currently no evidence that any intervention is beneficial for primary biliary cholangitis (PBC).”
  - Standard care guidelines for PBC usually recommended the use of ursodeoxycholic acid (UDCA).
  - This systemic review of these treatments (74 trials, 5902 participants) showed differences in these drugs when compared with no intervention in mortality and / or serious adverse events.

|                                | Mortality                                                    | Severe Adverse Events |
|--------------------------------|--------------------------------------------------------------|-----------------------|
| – Azathioprine                 | ↓                                                            | -                     |
| – D-penicillin                 | -                                                            | ↑                     |
| – Methotrexate                 | ↑                                                            | -                     |
| – UDCA plus obeticholic        |                                                              | ↑                     |
| <u>Drug vs No Intervention</u> |                                                              |                       |
| – Azathioprine                 | ↓ mortality                                                  |                       |
|                                | ▪ OR 0.56; 95% CI 0.32 to 0.98 (2 trials, 224 participants)  |                       |
| – Methotrexate                 | ↑ mortality                                                  |                       |
|                                | ▪ OR 8.83; 95% CI 1.01 to 76.96 (1 trial 60 participants)    |                       |
| – D-penicillamine              | ↑ severe adverse events                                      |                       |
|                                | ▪ OR 28.77; 95% CI 1.57 to 526.67 (1 trial, 52 participants) |                       |
| – Obeticholic acid plus UDCA   | Severe adverse events                                        |                       |
|                                | ▪ OR 3.58; 95% CI 1.02 to 12.51 (1 trial, 21.6 participants) |                       |

Bottom Lines:

- There is limited quality data on the optimal pharmacological treatment of primary biliary cholangitis (PBC).
- Alternate monotherapies or add-on combination therapy may increase mortality (methotrexate) or increase risk of severe adverse events (D-penicillamine, UDCA plus obeticholic acid).



## Primary Biliary Sclerosing Cholangitis (PSC)

Saffioti F, et al. Cochrane Library. Cochrane Database of Systemic Reviews 2017; 3. Art No: CD011343.

| Drug                         | Mortality Outcomes*             | Serious Adverse Events            |
|------------------------------|---------------------------------|-----------------------------------|
| ○ Colchicine vs placebo      | – OR 0.44; 95% CI 0.04% to 5.07 |                                   |
| ○ Corticosteroids vs placebo | – RR 3.32; 95% CI 0.71 to 15.62 | ▪ OR 20.00; 95% CI 0.93 to 429.90 |
| ○ Cyclosporin                | –                               | ▪ RR 2.64; 95% CI 0.99 to 7.03    |
| ○ Infliximab                 | –                               | ▪ RR 0.80; 95% CI 0.02 to 40.44   |
| ○ Penicillin in placebo      | – OR 1.18; 95% CI 0.39 to 3.58  | ▪ RR 13.60, 95% CI 0.78 to 237.83 |
| ○ UDCA**                     | – OR 1.51; 95% CI 0.71 to 15.62 | ▪ OR 1.22; 95% CI 0.68 to 2.17    |

\*no evidence in difference in clinical benefits such as need for liver transplantation or a reduction in the incidence proportion of cholangiocarcinoma

\*\*UDCA vs placebo improved health-related quality of life mean difference (MD) 1.30; 95% CI -5.61 to 8.21

### Bottom Lines:

- Despite there being 13 different interventions in 13 RCTs in 1211 participants, the authors of this Cochrane review conclude that “evidence is currently insufficient to show difference in effectiveness...between any active pharmacological intervention and no intervention for PBC.

## Hepatitis B Viral (HBV) Infection

Mantzoukis K, et al. Cochrane Library. Cochrane Database of Systemic Reviews 2017; 3. Art No: CD011645.

- Acute HBV infection
  - Of the agents studies (interferon, lamivudine, entecavir or HBIG) there was no ↑ risk of mortality at 1 yr
    - ↑ mortality at 1 yr
    - ↑ progression to fulminant liver disease / hepatic encephalopathy
    - ↑ progression from acute to chronic HBV infection
  - ↑ progression to fulminant liver disease / hepatic encephalopathy or progression from acute to chronic HBV infection.
  - Increase (↑)
    - Lamivudine vs placebo
      - OR 1.99; 95% CI 1.05 to 3.77 (3 trials, 285 participants)
    - Lamivudine vs entecavir
      - OR 3.64; 95% CI 1.31 to 10.13 (1 trials, 90 participants)
    - Interferon vs placebo
      - OR 348.16; 95% CI 45.39 to 2670.26 (2 trial, 200 participants)



- No increase (↑)
  - Entecavir vs no intervention
    - OR 0.58; 95% CI 0.23 to 1.49 (1 trial, 131 participants)

Bottom Lines:

- There was an increased risk of acute HBV infection progressing to chronic HBV when acute HBV was treated with lamivudine or interferon.

▪ Booster Vaccination to prevent HBV Infection

Poorolajal J, et al. Cochrane Library. Cochrane Database of Systemic Reviews 2016; 6. Art No: CD008256.

Bottom Lines:

- There were no eligible randomized clinical trials fulfilling the inclusion criteria of this review.

❖ Booster Vaccination to prevent HBV Infection

Sangkomkamhang US, et al. Cochrane Library. Cochrane Database of Systemic Reviews 2014; 11. Art No: CD007879.

- The two major sources of HBV infection are
  - Transmission from an infected mother
  - Living in an infected household
- The rate of perinatal transmission is high, and 3 maternal HBV vaccine immunizations can be given
  - To the mother before birth
  - To the infant after birth

Bottom Lines:

- There are “....no RCTs that have assessed the effect of HBV vaccine [given to the mother] during pregnancy for preventing infant [HBV] infection.”



## Hepatitis C Viral (HCV) Infection

Kalafateli M, et al. Cochrane Library. Cochrane Database of Systemic Reviews 2017; 3. Art No: CD011644.

### ➤ Acute HBV infection

- Pharmacological intervention for acute hepatitis C infection
  - ↓ progression to chronic HCV (lack of sustained virological response]) interferon-alpha vs no intervention
    - OR 0.27; 95% CI 0.09 to 0.76 (3 trials, 99 participants)
  - Serious adverse events higher with
    - Interferon-alpha or interferon-β vs no intervention
      - OR 2.03.70; 95% CI 9.01 to 4574.81 (1 trial, 33 participants) [IFN-α] and,
      - OR 27.88; 95% CI 1.48 to 526.12 (1 trial, 40 participant) [IFN-β])
    - Pegylated interferon-alpha (PegIFN-α) plus ribavirin vs PegIFN-α monotherapy
      - RR 2.74; 95% CI 1.40 to 5.33 (2 trials, 237 participants)

#### Bottom Lines:

- Interferon-alpha decreases the incidence of chronic HBV infection
  - The benefit was associated with increased risk of serious adverse events
- There is no data on the relevance of this ↓ SVR on other aspects of HBV infection (e.g., compensated or decompensated cirrhosis, need for liver transplantation, health-related quality of life); and SVR remains an “unvalidated surrogate outcome for HCV infection.”

### ➤ Chronic HBV infection

- Peginterferon plus ribavirin versus interferon plus ribavirin for chronic HCV infection

Hauser G, et al. Cochrane Library. Cochrane Database of Systemic Reviews 2014; 2. Art No: CD005441.

- PegIFN alpha 2a or PegIFN alpha 2b plus ribavirin vs interferon plus ribavirin
  - ↑ number of persons achieving sustained virological response (SVR) 50.7% vs 36.7% (RR 1.39; 95% CI 1.25 to 1.56), even when using trial sequential analysis.
  - ↑ adverse effects
    - Neutropenia 15.1% vs 7.1%
      - RR 2.15; 95% CI 1.76 to 2.61
    - Thrombocytopenia 5.8% vs 2.1%
      - RR 2.63; 95% CI 1.68 to 4.11
    - Arthralgia 29.7% vs 23.6%
      - RR 1.19; 95% CI 1.05 to 1.35
    - Injection site reaction 53.7% vs 28.7%
      - RR 1.71; 95% CI 1.50 to 1.93
    - Nausea 34.0% vs 28.6%
      - RR 1.13; 95% CI 1.01 to 1.26



Bottom Lines:

- PegIFN of interferon alpha or beta leads to an increased sustained virological response (SVR) in HCV infection, at the cost of increased adverse effects such as neutropenia and thrombocytopenia.
- “The clinical consequence of achieved sustained virological response {SVR} are unknown, as sustained virological response is still an invalidated surrogate marker for HCV infection.”

▪ Peginterferon alpha 2a versus peginterferon in chronic HCV infection

Hauser G, et al. Cochrane Library. Cochrane Database of Systemic Reviews 2014; 2. Art No: CD005642.

- PegIFN alpha 2a (PEgIFN-2a) vs pegylated interferon 2b (PegIFN-2b)
  - ↑ number of HCV patients with sustained virological response (SVR) 51% vs 43%
    - RR 1.12; 95% CI 1.06 to 1.18; 12 trials for genotypes 1 and 4, but not for 2 and 3
  - No clear evidence of a difference between PegIFN-2a vs PegIFN-2b for adverse effects
    - Trial sequential analysis
      - Unable to exclude a relative risk reduction of 20%

▪ Direct-acting antivirals (DAA) on the market or underdevelopment for chronic HCV infection

Jakobsen JC, et al. Cochrane Library. Cochrane Database of Systemic Reviews 2017; 9. Art No: CD012143.

- Direct acting antivirals on the market or under development (DAAs) vs control
  - ↓ risk of no SVR 54.1% vs 23.8%
    - RR 0.44; 95% CI 0.37 to 0.52 (32 trials, 6886 participants)
  - No ↑ adverse events 5.2% vs 5.6%
    - OR 0.95; 95% CI 0.75 to 1.15 (43 trials, 15,817 participants)
  - Insufficient information from trial sequential analysis to rule out a beneficial effect of DAAs in reducing serious adverse events by 20% except for
    - Simeprevir, ↓ risk of serious adverse events
      - OR 0.62; 95% CI 0.45 to 0.86

Bottom Lines:

- Direct acting agents increase the likelihood of sustained virological response (SVR) in HCV infection, and initial increased adverse events
- The long-term effects of DAA are known as also it is unknown the effects of SVR on clinical outcome such as compensated or decompensated cirrhosis, development of hepatocellular cancer, need for liver transplantation, mortality or morbidity.
- SVR is a surrogate marker for clinical improvement, but it has not yet been validated for this function.







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