Rapid Reviews

Des Leddin and David Morgan

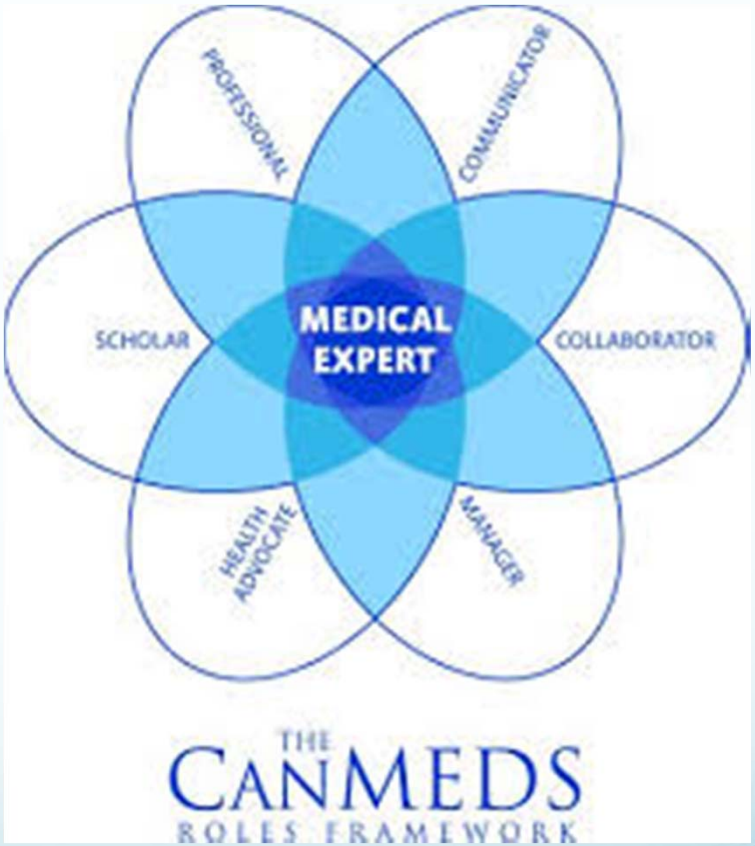
Disclosures

- Des Leddin
  - None
- David Morgan

- Speaker Bureau:
  - Pfizer, Merck, Astra Zeneca, Altana, Abbott, Janssen Ortho (JOI), Negma, Novartis, Sherring, Axcan, Wyeth, Proctor & Gamble, Solvay
- Consultant:
  - Pfizer, Merck, Astra Zeneca, Altana, Abbott, Janssen Ortho (JOI), Negma, Nycomed, Novartis, Sherring, Axcan, Wyeth, Proctor & Gamble, Solvay, Ferring, Lupin, Pendopharm, CCO
  - Microsoft
- Research Funding:
  - Heart and Stroke Foundation, Astra, JOI, Altana, Novartis, Pfizer, Negma,

CanMeds

- Expert 100%
  - Scholar 80%
  - Manager 20%



Objectives

- Become familiar with many of the highest impact articles in clinical GI in 2015
- Be able to decide whether selected publications answer your clinical need
- Be able to see if you and your peers agree

Methods

- Journals
  - Canadian Journal of Gastroenterology
  - Gastroenterology
  - American Journal
  - Gut
- Web of Science citations

AJG Hot January

- ACG Guidelines Colon Ischemia
- Quality Indicators for EGD
- Quality indicators Colonoscopy
- Quality indicators ERCP
- Quality indicators EUS
- Treatment of IBD
- State of Science summary Incontinence

Bloody diarrhea

- 82 year old female with acute onset pain and bloody diarrhea
- PH Hypertension, diabetes
- Physical

Q1 Suspected ischemia which of the following is true?

1. CT of the abdomen is not usually helpful

2. If IRCI is seen no further Ix is indicated

3. If pneumatosis is present CTA or angiography should be performed

4. A good outcome can be expected in patients with pain but no bleeding

CME

ACG Clinical Guideline: Epidemiology, Risk Factors, Patterns of Presentation, Diagnosis, and Management of Colon Ischemia (CI)

Lawrence J. Brandt, MD, MACG, AGAF, FASGE[1], Paul Feuerstadt, MD, FACG[2], George F. Longstreth, MD, FACG, AGAF[3] and Scott J. Boley, MD, FACS[4]

Am J Gastroenterol 2015; 110:18–44; doi:10.1038/ajg.2014.395; published online 23 December 2014

15 recommendations: Low or very low evidence in 15

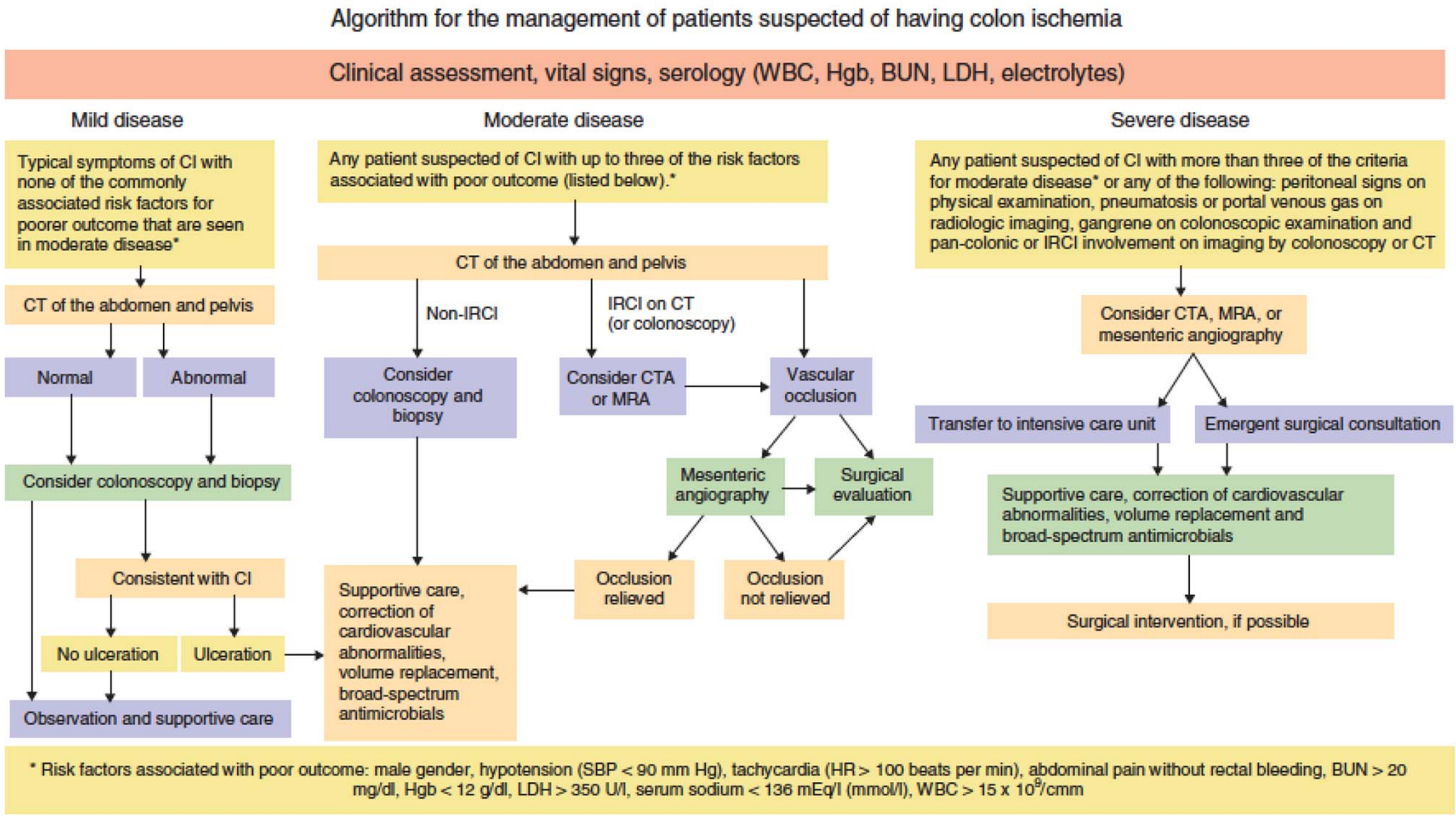


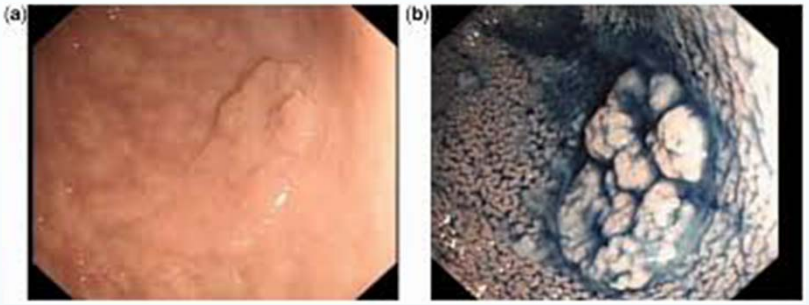
Figure 1. Diagnosis and treatment of colon ischemia (CI) based upon disease severity. BUN, blood urea nitrogen; CT, computed tomography; CTA, computed tomography angiography; Hgb, hemoglobin; IRCI, isolated right-colon ischemia; LDH, lactate dehydrogenase; MRI, magnetic resonance imaging; WBC, white blood cell count.

February

- ACG Clinical Guideline: Genetic Testing and Management of Hereditary Gastrointestinal Cancer Syndromes
- Incidence, Prevalence and trends of microscopic colitis. Meta-analysis
  - MC is a common disease process. Female gender, increased age, and the use of PPIs and SSRIs are associated with a significantly increased risk of developing MC. Further work is needed to evaluate reported data from developing countries and to elucidate the biologic mechanisms behind the risk
- Intestinal microbiota and diet in IBS.
  - Hypothesis

February

- Impact of Chromoscopy on Adenoma Detection in Patients With Lynch Syndrome: A Prospective, Multicenter, Blinded, Tandem Colonoscopy Study
  - The results support the proposition that chromocolonoscopy may significantly improve the detection rate of colorectal adenomas in patients undergoing screening or surveillance colonoscopy for Lynch syndrome

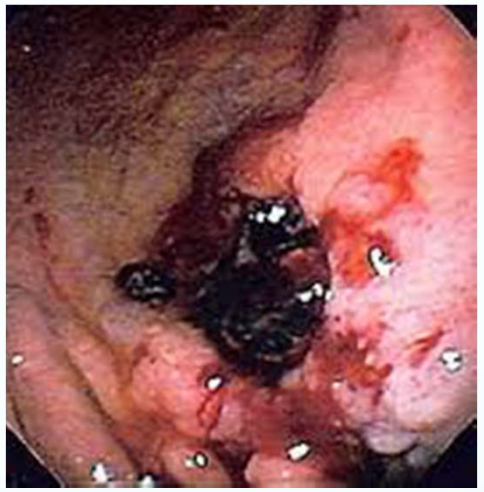


February

- Visceral Abdominal Obesity Is Associated With an Increased Risk of Irritable Bowel
  - Visceral adiposity measured by VAT, VAT/SAT, and waist circumference is associated with an increased risk of IBS, especially of IBS-D. However, neither SAT nor BMI are associated with an increased risk of IBS
- The Role of Chronic Norovirus Infection in the Enteropathy Associated With Common Variable Immunodeficiency
  - Norovirus is an important pathogen for patients with CVID and a cause of CVID Enteropathy, as viral clearance, symptom resolution, and histological recovery coincide. Ribavirin requires further evaluation as a potential therapy

Upper GI bleed

- 70 year old male
- Melena
- On warfarin, previous PE
- Endoscopy gastric ulcer
- Helicobacter negative, biopsies negative
- Home on PPI



Q2. With regard to warfarin which is true?

1. Restarting will increase risk of bleeding
2. Restarting will reduce risk of thromboembolism
3. Rebleeding is usually severe and requires ICU care
4. Anticoagulation should be discontinued after an episode of GIB

The Risks of Thromboembolism Vs. Recurrent Gastrointestinal Bleeding after Interruption Systemic Anticoagulation in Hospitalized Inpatients With Gastrointestinal Bleeding: A Prospective Study N. Sengupta et al

- OBJECTIVES: Anticoagulants carry a significant risk of gastrointestinal bleeding (GIB). Data regarding the safety of anticoagulation continuation/cessation after GIB are limited. We sought to determine the safety and risk of continuation of anticoagulation after GIB.

- METHODS: We conducted a prospective observational cohort study on consecutive patients admitted to the hospital who had GIB while on systemic anticoagulation. Patients were classified into two groups at hospital discharge after GIB: those who resumed anticoagulation (median 5 days) and those who had anticoagulation discontinued. Patients in both groups were contacted by phone 90 days after discharge to determine the following outcomes:
  - (i) thromboembolic events,
  - (ii) hospital readmissions related to GIB, and
  - (iii) mortality.

- Univariate and multivariate Cox proportional hazards were used to determine factors associated with thrombotic events, rebleeding, and death

- 197 patients developed GIB while on systemic anticoagulation (n =145, 74% on warfarin). Following index GIB, anticoagulation was discontinued in 76 patients (39%) at discharge.

- In-hospital transfusion requirements, need for intensive care unit care, and etiology of GIB were similar between the two groups.

- During the follow-up period, 7 (4%) patients suffered a thrombotic event and 27 (14%) patients were readmitted for GIB.

- Anticoagulation continuation was independently associated on multivariate regression with a lower risk of major thrombotic episodes within 90 days (hazard ratio (HR)=0.121, 95% confidence interval (CI)=0.006–0.812, P =0.03). Patients with any malignancy at time of GIB had an increased risk of thromboembolism in follow-up (HR=6.1, 95% CI=1.18–28.3, P =0.03).

- Anticoagulation continuation at discharge was not significantly associated with an increased risk of recurrent GIB at 90 days (HR=2.17, 95% CI=0.861–6.67, P =0.10) or death within 90 days (HR=0.632, 95% CI=0.216–1.89, P =0.40).

- CONCLUSIONS: Restarting anticoagulation at discharge after GIB was associated with fewer thromboembolic events without a significantly increased risk of recurrent GIB at 90 days. The benefits of continuing anticoagulation at discharge may outweigh the risks of recurrent GIB.

Details

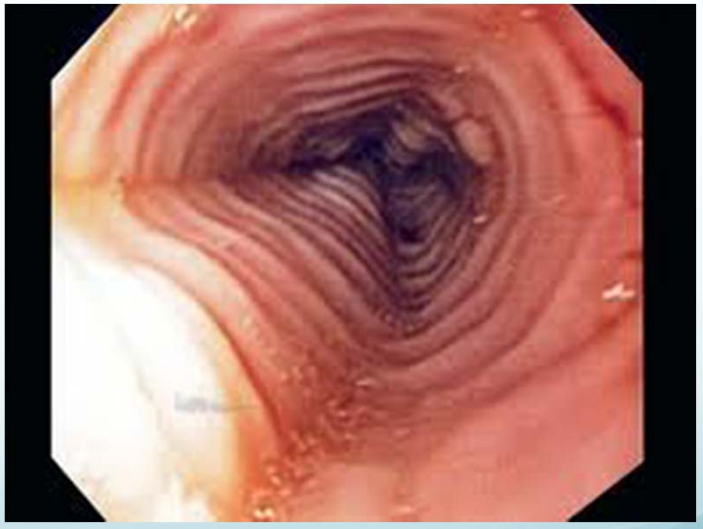
- Interruption - holding for 72 hours after discharge
- Continued - more likely to have prosthetic valve, prior TIA, prior UGI bleed
- Stopped -more likely malignancy
- Major decision to restart or not
- Bleeds tend to occur within 2 weeks, Thromboembolism 2-8 weeks so maybe hold for two weeks?

March

- Colonization With Toxicogenic C. Difficile Upon Hospital Admission, and Risk of Infection: A Systematic Review and Meta-Analysis
  - Over 8% of admitted patients are carriers of toxinogenic C. Difficile with an almost 6 times higher risk of infection. These findings update current knowledge regarding the contribution of colonization in CDI epidemiology and stress the importance of preventive measures toward colonized patients.
- Risk Factors on the Development of New-Onset Gastroesophageal Reflux Symptoms. A Population-Based Prospective Cohort Study: The HUNT Study
  - New-onset GERS were associated with increasing age, female sex, lower education, gain in BMI, and ever tobacco smoking. Tobacco smoking cessation was associated with new-onset GERS among those who gained weight upon quitting.

March

- How Do Gastroenterologists Assess Overall Activity of Eosinophilic Esophagitis in Adult Patients?
  - Gastroenterologists rate EoE activity mainly on the basis of endoscopic findings and symptoms and, to a lesser extent, on histologic findings.



March

- Impact of Retroflexion Vs. Second Forward View Examination of the Right Colon on Adenoma Detection: A Comparison Study
  - Retroflexion in the right colon can be safely achieved in the majority of patients undergoing colonoscopy for colorectal cancer screening. Reexamination of the right colon in either retroflexed or forward view yielded similar, incremental ADRs. A second exam of the right colon should be strongly considered in patients who have adenomas discovered in the right colon, particularly when endoscopist confidence in the quality of initial examination is low.

March

- A Prospective Randomized Controlled Study of Long-Term Combination Therapy Using Ursodeoxycholic Acid and Bezafibrate in Patients with Primary Biliary Cirrhosis and Dyslipidemia
  - Long-term combination therapy significantly improved the serum ALP levels and the Mayo risk score. However, the survival rate was not significantly different between the groups. In addition, long term combination therapy significantly increased the serum creatinine levels. We should pay close attention to adverse events during this long-term combination therapy.

March

- Characterization of Inflammation and Fibrosis in Crohn's Disease Lesions by Magnetic Resonance Imaging
  - MRI is accurate for detecting the presence of severe fibrosis in CD lesions on the basis of the enhancement pattern
- Trends and Racial/Ethnic Disparities in Gluten-Sensitive Problems in the United States: Findings from the National Health and Nutrition Examination Surveys From 1988 to 2012Trends and racial ethnic disparities in gluten sensitive in the US.
  - The overall prevalence of CD increased between 1988 and 2012 and is significantly more common in whites. In addition, a higher proportion of individuals maintaining a gluten-free diet in the absence of a diagnosis of CD are blacks.

March

- A Meta-Analysis of the Utility of C-Reactive Protein, Erythrocyte Sedimentation Rate, Fecal Calprotectin, and Fecal Lactoferrin to Exclude Inflammatory Bowel
  - CRP and Calprotectin of ≤0.5 or 40, respectively, essentially excludes IBD in patients with IBS symptoms. The addition of CRP and Calprotectin to symptom-based criteria may improve the confident diagnosis of IBS.

April

- Serrated Polyps and the Risk of Synchronous Colorectal Advanced Neoplasia: A Systematic Review and Meta-Analysis
  - Our meta-analysis showed that serrated polyps are associated with a more than twofold increased risk of detection of synchronous advanced neoplasia. Individuals with proximal and large serrated polyps have the highest risk. These individuals deserve surveillance colonoscopy.
- The Economic Impact of Clostridium difficile Infection: A Systematic Review
  - Forty-five COI studies quantified and confirmed the economic impact of CDI. Costing methods across studies were heterogeneous. Future studies should follow standard COI methodology, expand study perspectives (e.g., patient), and explore populations least studied (e.g., community-acquired CDI).

April

- Randomized Controlled Trial of Transoral Incision less Fundoplication Vs. Proton Pump Inhibitors for Treatment of Gastroesophageal Reflux Disease
  - Although TIF resulted in an improved GERD-related quality of life and produced a short-term improvement of the antireflux barrier in a selected group of GERD patients, no long-term objective reflux control was achieved.
- Inflammatory Bowel Disease in Immigrants to Canada and Their Children: A Population-Based Cohort Study
  - Younger age at arrival to Canada increased the risk of IBD in immigrants. Canadian-born children of immigrants from some regions assumed the high Canadian incidence of IBD, indicating that the underlying risk is activated with earlier life exposure to the Canadian environment in certain groups.

April

- Pregnancy and Postpartum Bowel Changes: Constipation and Fecal Incontinence
- The Spectrum of Constipation-Predominant Irritable Bowel Syndrome and Chronic Idiopathic Constipation: US Survey Assessing Symptoms, Care Seeking, and Disease Burden

Q3. With regard to C Diff which is true?

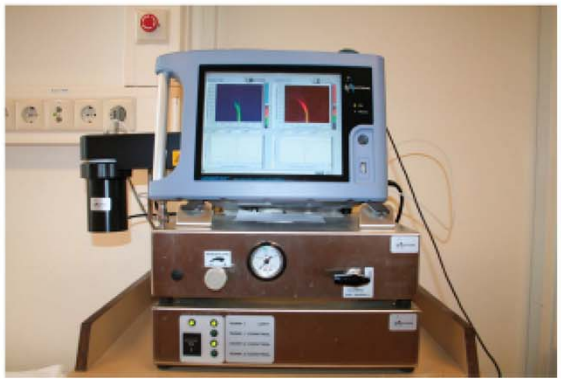
- 1. Average time to diagnosis is two days
- 2. Animal studies to detect VOCs have proven negative
- 3. Infection rates are declining
- 4. Bedside diagnosis may soon be possible using VOC

Rapid, Accurate, and On-Site Detection of C. difficile in Stool Samples Marije K. et al

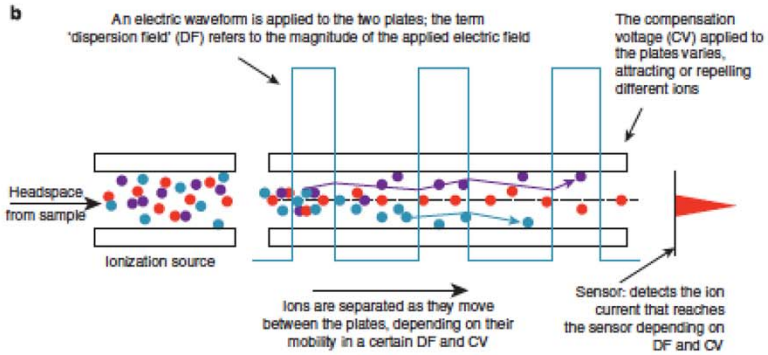
- OBJECTIVES: A rapid test to diagnose Clostridium difficile infection (CDI) on hospital wards could minimize common but critical diagnostic delay. Field asymmetric ion mobility spectrometry (FAIMS) is a portable mass spectrometry instrument that quickly analyses the chemical composition of gaseous mixtures (e.g., above a stool sample). Can FAIMS accurately distinguish C. difficile- positive from negative stool samples?

- METHODS: We analyzed 213 stool samples with FAIMS, of which 71 were C. difficile positive by microbiological analysis. The samples were divided into training, test, and validation samples. We used the training and test samples (n =135) to identify which sample characteristics discriminate between positive and negative samples, and to build machine learning algorithms interpreting these characteristics. The best performing algorithm was then prospectively validated on new, blinded validation samples (n =78). The predicted probability of CDI (as calculated by the algorithm) was compared with the microbiological test results (direct toxin test and culture).

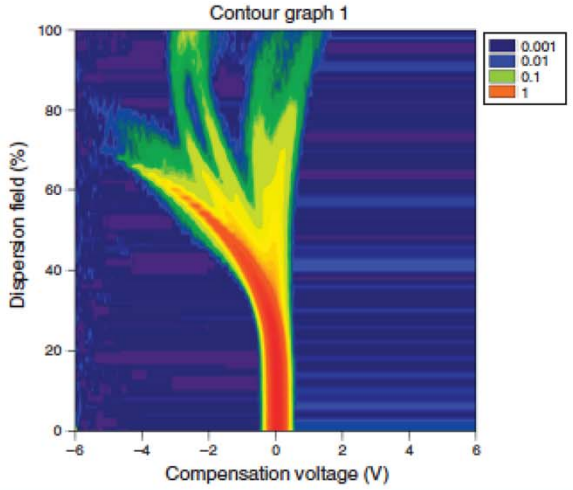
a



b


An electric waveform is applied to the two plates; the term 'dispersion field' (DF) refers to the magnitude of the applied electric field
The compensation voltage (CV) applied to the plates varies, attracting or repelling different ions
Headspace from sample
Ionization source
Ions are separated as they move between the plates, depending on their mobility in a certain DF and CV
Sensor: detects the ion current that reaches the sensor depending on DF and CV

c


Contour graph 1
0.001
0.01
0.1
1
Dispersion field (%)
100
80
60
40
20
0
−6
−4
−2
0
2
4
6
Compensation voltage (V)

FAIMS

- RESULTS: Using a Random Forest classification algorithm, FAIMS had a high discriminatory ability on the training and test samples (C-statistic 0.91 (95% confidence interval (CI): 0.86–0.97)). When applied to the blinded validation samples, the C-statistic was 0.86 (0.75–0.97). For samples analyzed ≤7 days of collection (n =76), diagnostic accuracy was even higher (C-statistic: 0.93 (0.85–1.00)). A cutoff value of 0.32 for predicted probability corresponded with a sensitivity of 92.3% (95% CI: 77.4–98.6%) and specificity of 86.0% (78.3–89.3%). For even fresher samples, discriminatory ability further increased.

- CONCLUSIONS: FAIMS analysis of unprocessed stool samples can differentiate between C. difficile- positive and negative samples with high diagnostic accuracy.

May

- ACG Clinical Guideline: Primary Sclerosing Cholangitis
- BOB CAT: A Large-Scale Review and Delphi Consensus for Management of Barrett's Esophagus With No Dysplasia, Indefinite for, or Low-Grade Dysplasia
  - In total, 80% of respondents agreed with 55 of 127 statements in the final voting rounds. Population endoscopic screening is not recommended and screening should target only very high-risk cases of males aged over 60 years with chronic uncontrolled reflux. A new international definition of BE was agreed upon. For any degree of dysplasia, at least two specialist gastrointestinal (GI) pathologists are required. Risk factors for cancer include male gender, length of BE, and central obesity.

May

- Peptic Ulcer Bleeding Risk: The Role of Helicobacter pylori Infection in NSAID/Low-Dose Aspirin Users
  - NSAID, low-dose ASA use, and H. pylori infection are three independent risk factors for the development of PUB, but there were differences in the interaction effect between low-dose ASA (no interaction) or NSAID (addition) use and H. pylori infection, which may have implications for clinical practice in prevention strategies.
- Local Recurrence After Endoscopic Resection for Large Colorectal Neoplasia: A Multicenter Prospective Study in Japan
  - En bloc ESD reduces the local recurrence rate for large colorectal neoplasias. Piecemeal resection is the most important risk factor for local recurrence regardless of the ER method used.

May

- A Randomized, Placebo-Controlled Trial of Lubiprostone for Opioid-Induced Constipation in Chronic Noncancer Pain
  - Lubiprostone significantly improved symptoms of OIC and was well tolerated in patients with chronic noncancer pain.
- Oral Prolonged Release Beclomethasone Dipropionate and Prednisone in the Treatment of Active Ulcerative Colitis: Results From a Double-Blind, Randomized, Parallel Group Study
  - BDP was non-inferior to PD in the treatment of active UC, with a good safety profile in both the groups.

Q4. PSC: which is true?

1. Liver biopsy is necessary for definitive diagnosis
2. Colonoscopy should be performed every 3-5 years
3. Urso in doses of >28 mg/kg offers best therapeutic option
4. Routine stenting after dilatation of a dominant stricture is not required

CME

ACG Clinical Guideline: Primary Sclerosing Cholangitis

Keith D. Lindor, MD, FACG[1,2], Kris V. Kowdley, MD, FACG[3] and M. Edwyn Harrison, MD[2]

Primary sclerosing cholangitis is a chronic cholestatic liver disease that can shorten life and may require liver transplantation. The cause is unknown, although it is commonly associated with colitis. There is no approved or proven therapy, although ursodeoxycholic acid is used by many on an empiric basis. Complications including portal hypertension, fat-soluble vitamin deficiency, metabolic bone diseases, and development of cancers of the bile duct or colon can occur.

Am J Gastroenterol 2015; 110:646–659; doi:10.1038/ajg.2015.112; published online 14 April 2015

24 recommendations : Low or very low evidence 11

ENDOSCOPIC MANAGEMENT

Recommendations

1. ERCP with balloon dilatation is recommended for PSC patients with dominant stricture and pruritus, and/or cholangitis, to relieve symptoms. (Strong recommendation, low quality of evidence) (64–68)
2. PSC with a dominant stricture seen on imaging should have an ERCP with cytology, biopsies, and fluorescence *in-situ* hybridization (FISH), to exclude diagnosis of cholangiocarcinoma. (Strong recommendation, low quality of evidence) (69,70)
3. PSC patients undergoing ERCP should have antibiotic prophylaxis to prevent post-ERCP cholangitis. (Conditional recommendation, low quality of evidence) (71)
4. Routine stenting after dilation of a dominant stricture is not required, whereas short-term stenting may be required in patients with severe stricture. (Conditional recommendation, low quality of evidence) (68,72)

PSC AND IBD

Recommendations

1. Annual colon surveillance preferably with chromoendoscopy is recommended in PSC patients with colitis beginning at the time of PSC diagnosis. (Conditional recommendation, moderate quality of evidence) (104)
2. A full colonoscopy with biopsies is recommended in patients with PSC regardless of the presence of symptoms to assess for associated colitis at time of PSC diagnosis. (Conditional recommendation, moderate quality of evidence) (3)
3. Some advocate repeating the exam every 3–5 years in those without prior evidence of colitis. (Weak recommendation, low quality of evidence) (3)

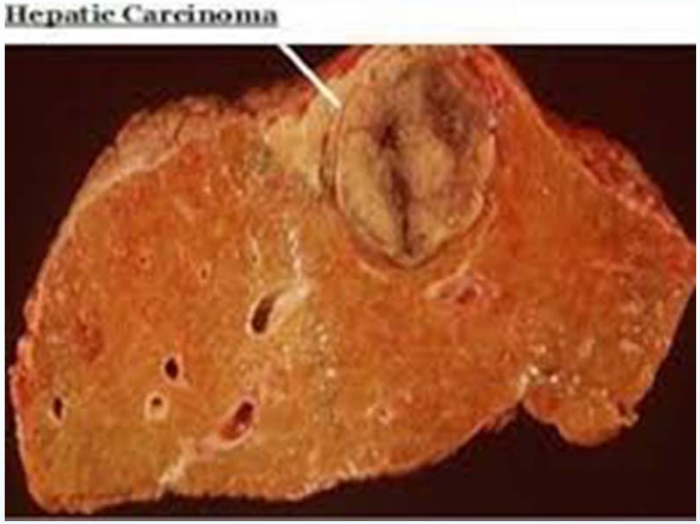
June

- C-Reactive Protein, Fecal Calprotectin, and Stool Lactoferrin for Detection of Endoscopic Activity in Symptomatic Inflammatory Bowel Disease Patients: A Systematic Review and Meta-Analysis
  - Although CRP, FC, and SL are useful biomarkers, their value in managing individual patients must be considered in specific clinical contexts.

- Utility of a Noninvasive Serum Biomarker Panel for Diagnosis and Monitoring of Eosinophilic Esophagitis: A Prospective Study
  - A panel of inflammatory factors known to be associated with EoE pathogenesis were not increased in the serum, nor were they responsive to therapy. None of these biomarkers are likely candidates for a serum test for EoE. Histologic analysis for diagnosis and management of EoE continues to be necessary, and novel, less invasive, biomarkers are needed.

June

- Alpha-Fetoprotein Measurement Benefits Hepatocellular Carcinoma Surveillance in Patients With Cirrhosis
  - The complementary use of AFP and US improved the effectiveness of HCC surveillance in patients with cirrhosis.



June

- Consecutive Monitoring of Fecal Calprotectin and Lactoferrin for the Early Diagnosis and Prediction of Pouchitis after Restorative Proctocolectomy for Ulcerative Colitis
  - Elevated fecal calprotectin and lactoferrin levels appeared to be significant predictors of pouchitis after restorative proctocolectomy for UC. Consecutive monitoring of these fecal biomarkers is useful for the early diagnosis of pouchitis.
- Identification of Pseudolysin (lasB) as an Aciduric Gluten-Degrading Enzyme with High Therapeutic Potential for Celiac Disease
  - Pseudolysin was identified as an enzyme cleaving gluten effectively at extremely low as well as near- neutral pH values. The potential to degrade gluten during gastric transport opens possibilities for its application as a novel therapeutic agent for the treatment of CD.

June

- Cyst Fluid Glucose Is Rapidly Feasible and Accurate in Diagnosing Mucinous Pancreatic Cysts
  - Glucose, whether measured by a laboratory assay, a glucometer, or a reagent strip, is significantly lower in mucinous cysts compared with non-mucinous pancreatic cysts
- Kolho et al. Helsinki. Fecal Microbiota in Pediatric Inflammatory Bowel Disease and Its Relation to Inflammation
  - Reduced microbial richness, fewer butyrate producers, abundance of Gram positive. Treatment with anti TNF restores a more normal diversity
  - Intestinal microbiota represents a potential biomarker for correlating the level of inflammation and therapeutic responses to be further validated.

Q 5. With regard to Fcal and endo recurrence which is true?

- 1. Produced exclusively by granulocytes
- 2. Levels correlate poorly with endoscopic recurrence
- 3. Combined measurement with hs CRP improves performance
- 4. Measurement may reduce need for colonoscopy by 30%

Levels of Fecal Calprotectin Are Associated With the Severity of Postoperative Endoscopic Recurrence in Asymptomatic Patients With Crohn's Disease Gilles Boschetti et al

- OBJECTIVES: Fecal calprotectin (fCal) is widely used as marker of gut inflammation and is strongly associated with the severity of endoscopic lesions in Crohn's disease (CD). We analyzed the relationships between levels of fCal and high-sensitivity C-reactive protein (hsCRP) and the presence and severity of postoperative endoscopic recurrence in asymptomatic CD patients (Harvey–Bradshaw index≤3).

- METHODS: Blood and fecal samples were collected in consecutive asymptomatic CD patients (Harvey–Bradshaw index 0.85±0.19, mean±s.e.m.) who had undergone an ileocolonic resection. hsCRP and fCal were measured and a routine ileocolonoscopy was performed within 18 months (median 7 months) from resection, to detect endoscopic recurrence according to the Rutgeerts score.

RESULTS: Eighty-six patients were included in this prospective multicenter observational cohort. fCal concentrations differed significantly in patients with endoscopic recurrence when compared with those in endoscopic remission (mean±s.e.m.: 473±78 µ g/g vs. 115±18 µ g/g; P <0.0001). The area under the receiver operating characteristic (ROC) curve to discriminate between patients in endoscopic remission and recurrence was 0.86 for fCal and lower for hsCRP (0.70). The best cutoff point for fCal to distinguish between endoscopic remission and recurrence was 100 µ g/g as determined by the ROC curve, and its sensitivity, specificity, positive and negative predictive values (NPVs), as well as overall accuracy were 95%, 54%, 69%, 93%, and 77%, respectively.

CONCLUSION: Measurement of fCal concentrations is a promising and useful tool for monitoring asymptomatic CD patients after ileocolonic resection. Taking into account the high NPV of fCal, a threshold below
100 µ g/g could avoid systematic ileocolonoscopies in 30% of patients from this population.

Details

- 43/86 had recurrent disease
- 78% ileal disease
- Overall accuracy for fCal (77%) better than hsCRP (53%)
- Levels of fCal correlated with severity of reurrence
- Combination of fCal and hsCRP not better than fCal alone

July

- Chromoendoscopy for surveillance in IBD
  - Despite compelling evidence from randomized trials, implementation of chromoendoscopy for IBD surveillance did not increase dysplasia detection compared with WLE with targeted and random biopsies. Retrospective.

- Diagnosis of Esophageal Motility Disorders: Esophageal Pressure Topography vs.Conventional Line Tracing
  - Superior inter-rater agreement and diagnostic accuracy of esophageal motility diagnoses were demonstrated with analysis using EPT over CLT among our selected raters. On the basis of these findings, EPT may be the preferred assessment modality of esophageal motility.

July

- The Relationship Among Perceived Stress, Symptoms, and Inflammation in Persons With Inflammatory Bowel Disease
  - Symptomatic disease activity was unrelated to intestinal inflammation in CD and only weakly associated in UC. Although there was a strong relationship between perceived stress and gastrointestinal symptoms, perceived stress was unrelated to concurrent intestinal inflammation. Longitudinal investigation is required to determine the directionality of the relationship between perceived stress, inflammation, and symptoms in IBD.

July

- Effects of Sapropterin on Portal and Systemic Hemodynamics in Patients With Cirrhosis and Portal Hypertension: A Bicentric Double-Blind Placebo-Controlled Study
  - Sapropterin, an oral synthetic analogue of BH4, at the used dose did not reduce portal pressure in patients with cirrhosis. Sapropterin was safe and no serious adverse effects or deleterious systemic hemodynamic effects were observed.

July

- Chromoendoscopy for Surveillance in Inflammatory Bowel Disease Does Not Increase Neoplasia Detection Compared With Conventional Colonoscopy With Random Biopsies: Results From a Large Retrospective Study
  - Despite compelling evidence from randomized trials, implementation of chromoendoscopy for IBD surveillance did not increase dysplasia detection compared with WLE with targeted and random biopsies.

- Forty-Year Analysis of Colonoscopic Surveillance Program for Neoplasia in Ulcerative Colitis: An Updated Overview
  - 15,000 patient years. Increase in dysplasia detection secondary to chromoendoscopy. Increase in colon ca recently. Decrease in colectomy for dysplasia Colonoscopic surveillance may have a signifi cant role in reducing the risk of advanced and interval CRC while allowing more patients to retain their colon for longer. Given the ongoing risk of early CRC, patients with any grade of dysplasia who are managed endoscopically should be monitored closely with advanced techniques.

July

- Anxiety and Depression Increase in a Stepwise Manner in Parallel With Multiple FGIDs and Symptom Severity and Frequency
  - Psychiatric comorbidity is common in patients referred to a secondary care center but is often unrecognized. The prevalence of both anxiety and depression is influenced by gender, presence of organic diseases, and FGIDs, and it increases with the number of coexistent FGIDs and frequency and severity of GI symptoms.

July

- Low Prevalence of Colon Polyps in Chronic Inflammatory Conditions of the Colon
  - Case control. Chronic inflammatory conditions of the colon are associated with a decreased prevalence of colon polyps. Lower in IBD and microscopic colitis
- Predictors and Significance of Incomplete Mucosal Recovery in Celiac Disease After 1 Year on a Gluten-Free Diet
  - The presence of more severe disease in terms of histology, serology, and signs of malabsorption was associated with histological non-response. In patients with high dietary adherence, incomplete villous recovery after 1 year does not affect the clinical response or long-term prognosis. A personalized approach is required to decide the optimal timing of the follow-up biopsy.
  - Lower in more severe, higher antibody levels, malabsorption. Complete in 68%

August

- Recurrent Alcoholic Cirrhosis in Severe Alcoholic Relapse After Liver Transplantation: A Frequent and Serious Complication
  - 700 patients, relapse in 18%, recurrent cirrhosis 6%. RAC occurs in <6% of ALD transplant patients. One-third of severe alcoholic relapse patients develop RAC <5 years after transplantation with a very poor prognosis.

- Prevalence of Cirrhosis in Hepatitis C Patients in the Chronic Hepatitis Cohort Study (CHeCS): A Retrospective and Prospective Observational Study
  - A high proportion of patients with biopsy-confirmed cirrhosis are not assigned ICD-9 codes for cirrhosis. Consequently, ICD-9 codes may not be reliable as the sole indicator of the prevalence of cirrhosis in cohort studies. Use of additional parameters suggests a fourfold higher prevalence of cirrhosis than is revealed by biopsy alone. These findings suggest that cirrhosis in CHC patients may be significantly underdocumented and underdiagnosed.

August

- Treatment of Chronic HCV With Sofosbuvir and Simeprevir in Patients With Cirrhosis and Contraindications to Interferon and/or Ribavirin
  - Sustained virologic response in 81%. The combination of SMV and SOF achieves high rates of SVR in patients with advanced cirrhosis but is lower with worsening Child class.

August

- Prevalence of Abnormal Liver Function Tests in Celiac Disease and the Effect of a Gluten-Free Diet in the US Population
  - Forty percent of individuals will have elevated LFTs at CD diagnosis; however, the majority will normalize with standard CD therapy. LFTs should be checked in all patients with CD and coexisting liver disorder should be considered in patients whose LFTs have not improved within a year on a GFD.
  - 40% elevated at diagnosis, 24% treated.
- The Clinical Utility of a Novel Blood-Based Multi-Transcriptome Assay for the Diagnosis of Neuroendocrine Tumors of the Gastrointestinal Tract
  - This study demonstrates that a blood-based multianalyte NET gene transcript measurement of well- differentiated small intestinal and pancreatic neuroendocrine tumor disease is sensitive and specific and outperforms the current monoanalyte diagnostic strategy of plasma CgA measurement.

August

- Impact of Statin Use on Survival in Patients Undergoing Resection for Early-Stage Pancreatic Cancer
  - The effects of statins varied by agent and dose. Active use of moderate-high-dose simvastatin at baseline was associated with improved overall and disease-free survival among patients undergoing resection for pancreatic cancer. Retrospective cohort. Improved survival

Q 6. With regard to Derm complications of anti TNF in IBD which is true?

- 1. Cumulative incidence was >25% at 5 years
- 2. Older age is associated with increased risk
- 3. In switching antiTNF for psoriasis recurrence in >80%
- 4.Risk of derm lesions is not dose related

Cumulative Incidence of, Risk Factors for, and Outcome of Dermatological Complications of Anti-TNF Therapy in Inflammatory Bowel Disease: A 14-Year Experience Estelle Fréling et al

- OBJECTIVES: The broader and prolonged use of anti-tumor necrosis factor (TNF) agents in inflammatory bowel disease (IBD) could expose patients to an increased risk of adverse reactions, including dermatological complications. We assessed the cumulative incidence of anti-TNF-induced cutaneous adverse reactions in IBD patients, their risk factors, their dermatological management, and their outcome in a large cohort of IBD patients.

- METHODS: In a single-center observational retrospective study, including all consecutive adult IBD patients treated with an anti-TNF agent between 2001 and 2014, all patients with dermatological complications under anti-TNF therapy were identified in a well-defined cohort of IBD patients. We conducted a survival analysis to determine the cumulative incidence of dermatological complications and risk factors for developing any dermatological complications, cutaneous infections, and psoriasiform lesions. Survival curves were estimated by the Kaplan–Meier method, and we used a Cox proportional hazards model to test the association between parameters and time to each event: any dermatological complication, cutaneous infections, and psoriasis lesions.

RESULTS: Among 583 IBD patients, 176 dermatological complications occurred, involving 20.5% of patients. Median duration of follow-up was 38.2 months (range: 1–179). Psoriasiform lesions (10.1%; 59/583) and cutaneous infections (11.6%, 68/583) were the most frequently observed, with a cumulative incidence of, respectively, 28.9% and 17.6% at 10 years. They led to anti-TNF discontinuation, respectively, in 18.6% and 2.9% of patients. In case of switching to another anti-TNF agent for psoriasiform lesions, recurrence occurred in 57% of patients. Ulcerative colitis was associated with a lower risk of developing cutaneous infections than Crohn's disease (hazard ratio (HR)=0.25; 95% confidence interval (CI)=0.09–0.68; P =0.007). Higher dosing of anti- TNF agent was associated with a higher risk of developing cutaneous infections (HR=1.99; 95% CI=1.09–3.64; P =0.025). A younger age at time of anti-TNF initiation was associated with a higher risk of dermatological complications (HR=2.25; 95% CI=1.39–3.62; P <0.001).

CONCLUSIONS: Dermatological complications involve one of fi ve patients treated with anti-TNF therapy after a
14-year follow-up. Association of cutaneous infections with higher anti-TNF dosing suggests a dose-dependent effect. Discontinuation of anti-TNF therapy due to dermatological complications is required in one out of five patients with psoriasiform lesions, but specific dermatological treatment allows to continue anti-TNF therapy in half of them

September

- Prevalence and Severity of Nonalcoholic Fatty Liver Disease in Non-Obese Patients: A Population Study Using Proton-Magnetic Resonance Spectroscopy
  - One-fifth of the general non-obese Chinese population has NAFLD. Non-obese patients with NAFLD do not have a higher risk of steatohepatitis or advanced fibrosis. Patients with risk factors of advanced fibrosis such as metabolic syndrome and PNPLA3 G allele carriage should be assessed for severe NAFLD.

September

- Cost-Effective Evaluation of Nonalcoholic Fatty Liver Disease With NAFLD Fibrosis Score and Vibration Controlled Transient Elastography
  - Non-invasive risk stratification with both the NFS alone and the NFS/VCTE are cost-effective strategies for the evaluation and management of patients with NAFLD presenting to a gastroenterologist. Further research is needed to better define the natural history of NAFLD and the effect of novel treatments on decision making.

September

- Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE):Determining Therapeutic Goals for Treat-to-Target
  - The group agreed upon 12 recommendations for ulcerative colitis (UC) and Crohn's disease (CD). The agreed target for UC was clinical/patient-reported outcome (PRO) remission (defined as resolution of rectal bleeding and diarrhea/altered bowel habit) and endoscopic remission (defined as a Mayo endoscopic subscore of 0–1). Histological remission was considered as an adjunctive goal. Clinical/ PRO remission was also agreed upon as a target for CD and defined as resolution of abdominal pain and diarrhea/altered bowel habit; and endoscopic remission, defined as resolution of ulceration at ileocolonoscopy, or resolution of findings of inflammation on cross-sectional imaging

September

- Altered Colonic Bacterial Fermentation as a Potential Pathophysiological Factor in Irritable Bowel Syndrome
  - Colonic intraluminal pH is decreased, suggesting higher colonic fermentation, in IBS patients compared with HC. Fecal SCFAs are not a sensitive marker to estimate intraluminal bacterial fermentation.

September

- Impact of Screening Program on Incidence of Colorectal Cancer: A Cohort Study in Italy
  - A total of 171,785 people have been invited, and approximately 70% have undergone FIT at least once (272,197 tests). The rate of colonoscopy participation has been about 90%, and 2896 cancers have been recorded (1237 in the screening period). The age-adjusted and sex-adjusted incidence rate ratios as compared with pre-screening were 1.60 (95% confidence interval (CI), 1.43–1.79), 0.86 (95% CI, 0.78–0.94), and 0.59 (95% CI, 0.50–0.69) for the first round, subsequent rounds, and post screening, respectively. Cumulative incidence and incidence-based mortality decreased by 10% (95% CI, 3–17%) and 27% (95% CI, 15–37%), respectively

Q7. With regard to small bowel bleeding which is true?

- 1. Barium studies should be performed at baseline
- 2. Given the low detection of proximal lesions with VCE push endoscopy should be performed
- 3. Patients with Heyde's syndrome should be managed medically
- 4. MR is preferred over CTE especially in older patients

CME

ACG Clinical Guideline: Diagnosis and Management of Small Bowel Bleeding

Lauren B. Gerson, MD, MSc, FACG[1], Jeff L. Fidler, MD[2], David R. Cave, MD, PhD, FACG[3] and Jonathan A. Leighton, MD, FACG[4]

31 recommendations: Low or very low evidence in 21

Diagnosis of small bowel bleeding

1. Second-look upper endoscopy should be considered in cases of recurrent hematemesis, melena, or a previously incomplete exam (strong recommendation, low level of evidence).
2. Second-look colonoscopy should be considered in the setting of recurrent hematochezia or if a lower source is suspected (conditional recommendation, very low level of evidence).
3. If the second-look examinations are normal, the next step should be a small bowel evaluation (strong recommendation, moderate level of evidence).
4. Push enteroscopy can be performed as a second-look examination in the evaluation of suspected small bowel bleeding (conditional recommendation, moderate level of evidence).
5. Video capsule endoscopy (VCE) should be considered as a first-line procedure for SB evaluation after upper and lower GI sources have been excluded, including second-look endoscopy when indicated (strong recommendation, moderate level of evidence).
6. Owing to the lower detection rate of lesions in the duodenum and proximal jejunum with VCE, push enteroscopy should be performed if proximal lesions are suspected (strong recommendation, very low level of evidence).
7. Total deep enteroscopy should be attempted if there is a strong suspicion of a small bowel lesion based on clinical presentation (strong recommendation, moderate level of evidence).
8. Any method of deep enteroscopy can be used when endoscopic evaluation and therapy is required based on similar diagnostic yields (strong recommendation, high level of evidence).
9. Intraoperative enteroscopy is a highly sensitive but invasive diagnostic and effective therapeutic procedure. Its usage should be limited to scenarios where enteroscopy cannot be performed, such as patients with prior surgeries and intestinal adhesions (strong recommendation, low level of evidence).
10. VCE should be performed before deep enteroscopy to increase diagnostic yield. Initial deep enteroscopy can be considered in cases of massive hemorrhage or when VCE is contraindicated (strong recommendation, high level of evidence).

Usage of radiographic examinations

11. Barium studies should not be performed in the evaluation of small bowel bleeding (strong recommendation, high level of evidence).
12. Computed tomographic enterography (CTE) should be performed in patients with suspected small bowel bleeding and negative capsule endoscopy because of higher sensitivity for the detection of mural-based small bowel masses, superior capability to locate small bowel masses, and ability to guide subsequent deep enteroscopy (strong recommendation, low level of evidence).
13. CT is preferred over magnetic resonance (MR) imaging for the evaluation of suspected small bowel bleeding. MR can be considered in patients with contraindications for CT or to avoid radiation exposure in younger patients (conditional recommendation, very low level of evidence).
14. CTE could be considered before VCE in the setting of established inflammatory bowel disease, prior radiation therapy, previously small bowel surgery, and/or suspected small bowel stenosis (strong recommendation, very low level of evidence).
15. In patients with suspected small bowel bleeding and negative VCE examination, CTE should be performed if there is high clinical suspicion for a small bowel source despite performance of a prior standard CT of the abdomen (conditional recommendation, very low level of evidence).
16. In acute overt massive GI bleeding, conventional angiography should be performed emergently for hemodynamically unstable patients (strong recommendation, low level of evidence).
17. In hemodynamically stable patients with evidence of active bleeding, multiphasic CT (CTA) can be performed to identify the site of bleeding and guide further management (strong recommendation, low level of evidence).
18. In patients with acute overt GI bleeding and slower rates of bleeding (0.1–0.2 ml/min), or uncertainty if actively bleeding, tagged red blood cell scintigraphy should be performed if deep enteroscopy or VCE are not performed to guide timing of angiography (strong recommendation, moderate level of evidence).

19. In brisk active overt bleeding, CT angiography (CTA) is preferred over CTE (conditional recommendation, very low level of evidence).
20. Conventional angiography should not be performed as a diagnostic test in patients without overt bleeding (conditional recommendation, very low level of evidence).
21. Provocative angiography can be considered in the setting of ongoing overt bleeding and negative VCE, deep enteroscopy, and/or CT examination (conditional recommendation, very low level of evidence).
22. In younger patients with ongoing overt bleeding and normal testing with capsule endoscopy and enterography examinations, a Meckel's scan should be performed (conditional recommendation, very low level of evidence).

Treatment and outcomes

23. If a source of bleeding is found by VCE and/or deep enteroscopy in the small intestine that is associated with significant ongoing anemia or active bleeding, then the patient should be managed with endoscopic therapy (strong recommendation, low level of evidence).
24. If after appropriate small bowel investigation no source of bleeding is found, the patient should be managed conservatively with oral iron or by intravenous infusion as is dictated by the severity and persistence of the associated iron-deficiency anemia. In this context, a small vascular lesion found on capsule endoscopy does not always need treatment (strong recommendation, very low level of evidence).

October

- Clinical and Pathophysiological Consequences of Alterations in the Microbiome in Cirrhosis
- The Clinical Impact of Immediate On-Site Cytopathology Evaluation During Endoscopic Ultrasound-Guided Fine Needle Aspiration of Pancreatic Masses: A Prospective Multicenter Randomized Controlled Trial
  - Results of this study demonstrated no significant difference in the diagnostic yield of malignancy, proportion of inadequate specimens, and accuracy in patients with pancreatic mass undergoing EUS–FNA with or without OCE.

October

- Spatial Predisposition of Dysplasia in Barrett's Esophagus Segments: A Pooled Analysis of the SURF and AIM Dysplasia Trials
  - The post hoc analysis of two RCTs reveals a substantially increased prevalence of dysplasia proximally in BE segments. Our simulations suggest an altered biopsy regimen could increase sensitivity of biopsies in short-segment BE by >30%.
- SOX2 as a Novel Marker to Predict Neoplastic Progression in Barrett's Esophagus
  - SOX2 expression is lost during transition from nondysplastic BE to HGD/EAC, and it is associated with an increased risk of neoplastic progression. The highest PV is achieved by concurrent loss of SOX2 and aberrant p53 expression in BE patients with LGD. The use of these markers has the potential to significantly improve risk stratification of Barrett surveillance.

October

- Infections and Risk of Celiac Disease in Childhood: A Prospective Nationwide Cohort Study
  - This is the first large-scale population-based cohort study of this association. Our results are in line with immunological data suggesting that early life infections may have a role in CD development. However, non-causal explanations for this association due to surveillance bias and reverse causation cannot be excluded.
- Are ESPGHAN “Biopsy-Sparing” Guidelines for Celiac Disease Also Suitable for Asymptomatic Patients
  - If confirmed in large multicenter prospective studies, the “biopsy-sparing” protocol seems to be applicable to both symptomatic and asymptomatic patients with anti-tTG titer ≥10 times ULN, positive EMA, and HLA-DQ2/DQ8.

October

- Elevated Serum Triglycerides Are Independently Associated With Persistent Organ Failure in Acute Pancreatitis
  - Elevated serum TGs in AP patients are independently and proportionally correlated with persistent organ failure regardless of etiology. TG-mediated lipotoxicity may be an attractive target to design novel interventions for severe AP.

November

- Risk of Celiac Disease in the First- and Second-Degree Relatives of Patients With Celiac Disease: A Systematic Review and Meta-Analysis
  - Pooled prevalence of CD among FDRs is 7.5% and varies considerably with their relationship with the index patient. The risk of CD in FDRs also varies according to gender and geographical location.
- Autofluorescence-Directed Confocal Endomicroscopy in Combination With a Three-Biomarker Panel Can Inform Management Decisions in Barrett's Esophagus
  - The combination of pCLE on AFI-targeted areas and a 3-biomarker panel identifies patients with dysplasia.

November

- Management and Outcomes of Esophageal Perforation: A National Study of 2,564 Patients in England
  - This study provides evidence for the centralization of management of esophageal perforation to high volume centers with appropriate multi-disciplinary infrastructure to treat these complex patients.

November

- Morbid Obesity Is Associated With Adverse Clinical Outcomes in Acute Pancreatitis: A Propensity-Matched Study
  - Morbid obesity negatively influences inpatient hospitalization and is associated with adverse clinical outcomes, including mortality, organ failure, and health-care resource utilization. These observations and the increasing global prevalence of obesity justify ongoing efforts to understand the role of obesity-induced inflammation in the pathogenesis and management of AP.

November

- Right Or Left in COLonoscopy (ROLCOL)? A Randomized Controlled Trial of Right- versus Left-Sided Starting Position in Colonoscopy
  - Our study reveals that right-sided positioning at the start of colonoscopy results in more comfortable and quicker procedures. Of the factors identified by multiple linear regression to independently have an impact on time to reach the cecum, only starting position is modifiable. Right-sided starting position may therefore be of benefit in colonoscopy, in particular for women and patients who have previously undergone abdominal surgery.
- Inflammatory Bowel Disease Patients Are at Increased Risk of Invasive Pneumococcal Disease: A Nationwide Danish Cohort Study 1977–2013
  - The risk of IPD is significantly increased both before and after diagnosis of IBD, with limited impact of IBD medications. This suggests that the risk of IPD in patients with IBD is related to the underlying altered immune response in these patients.

November

- Temporal Trends in the Incidence and Natural History of Diverticulitis: A Population-Based Study
  - The incidence of diverticulitis has increased by 50% in 2000–2007 compared with 1990–1999, and more so in younger people. Complications are relatively uncommon. Recurrent diverticulitis is frequent but typically uncomplicated. Younger people with diverticulitis have less severe disease, more recurrence, and better survival.

December

- Interval Colorectal Cancer After Colonoscopy: Exploring Explanations and Solutions
  - There is good evidence that colorectal cancer (CRC) screening has been successful at reducing both CRC incidence and death. Colonoscopy, utilized as either a primary screening tool or a follow-up exam when other screening tests are positive, has significantly contributed to these encouraging trends. However, it is well recognized that colonoscopy is not perfectly sensitive for the detection of neoplasia and that CRC can be diagnosed within a short interval following a colonoscopy that did not detect one. The literature surrounding these cases has rapidly expanded over the last decade. Specifically, studies aimed at understanding the frequency of these events and the likely explanations for their occurrence have been performed. This review will highlight current knowledge around the epidemiology of interval post colonoscopy CRC (PCCRC). The common explanations for these cancers including missed lesions, new lesions, and incompletely resected lesions will be reviewed and their contribution to interval PCCRC estimated. Finally, the relationship of these putative explanations to potential opportunities to prevent interval PCCRC will be explored. Current approaches to prevention largely center on consistent adherence to quality colonoscopy standards. Future approaches include advances in technology to better visualize the colon and adequately resect detected neoplasia. Finally, improvement in training as well as development of a culture of continuous quality improvement will be essential to maximize the benefits of colonoscopy in daily clinical practice

December

- Cost Utility of Competing Strategies to Prevent Endoscopic Transmission of Carbapenem-Resistant Enterobacteriaceae
  - In institutions with a low CRE prevalence, ERCP with FDA-recommended reprocessing is the most cost-effective approach for mitigating CRE transmission risk. Only in settings with an extremely high CRE prevalence did ERCP with culture and hold become cost-effective.

- Inflammatory Bowel Disease Patients' Willingness to Accept Medication Risk to Avoid Future Disease Relapse
  - IBD patients are willing to accept high levels of lymphoma and serious infection risk to maintain disease remission. These preferences are congruent with the treatment paradigms emphasizing mucosal healing and early aggressive therapy and highlight patients' strong preferences for therapies resulting in durable remission of at least 5 years.

December

- Colonic Diverticula Are Not Associated With an Increased Risk of Colorectal Adenomas
  - Patients with colonic diverticula do not have an increased risk of colorectal adenomas or advanced adenomas.
- Risk of Diabetes Mellitus After First-Attack Acute Pancreatitis: A National Population-Based Study
  - The risk of diabetes increases by twofold after AP; therefore, a long-term screening is necessary to evaluate diabetes after an attack regardless of severity. Further research should be conducted to develop cost-effective follow-up strategies, and to elucidate the underlying mechanisms of the relationship between diabetes and **AP.**

December

- Admission Hematocrit and Rise in Blood Urea Nitrogen at 24 h Outperform Other Laboratory Markers in Predicting Persistent Organ Failure and Pancreatic Necrosis in Acute Pancreatitis: A Post Hoc Analysis of Three Large Prospective Databases
  - Admission hematocrit ≥44% and rise in BUN at 24h may be the optimal predictive tools in clinical practice among existing laboratory parameters and scoring systems.

Q 8. With regard to colonic polyps which is true?

- 1. The majority of small polyps detected by CT will progress within 3 years
- 2. Small polyps may regress 40% of time
- 3. Polyps which grow are more likely to be advanced adenomas
- 4. After 3 years 5-10% of small polyps demonstrate high grade dysplasia

Evolution of Screen-Detected Small (6–9 mm) Polyps After a 3-Year Surveillance Charlotte J. Tutein Nolthenius

- OBJECTIVES : Volumetric growth assessment has been proposed for predicting advanced histology at surveillance computed tomography (CT) colonography (CTC). We examined whether is it possible to predict which small (6–9 mm) polyps are likely to become advanced adenomas at surveillance by assessing volumetric growth.

- METHODS: In an invitational population-based CTC screening trial, 93 participants were diagnosed with one or two 6–9 mm polyps as the largest lesion(s). They were offered a 3-year surveillance CTC. Participants in whom surveillance CTC showed lesion(s) of ≥6 mm were offered colonoscopy. Volumetric measurements were performed on index and surveillance CTC, and polyps were classified into growth categories according to ±30% volumetric change (>30% growth as progression, 30% growth to 30% decrease as stable, and >30% decrease as regression). Polyp growth was related to histopathology.

RESULTS: Between July 2012 and May 2014, 70 patients underwent surveillance CTC after a mean surveillance interval of 3.3 years (s.d. 0.3; range 3.0–4.6 years). In all, 33 (35%) of 95 polyps progressed, 36 (38%) remained stable, and 26 (27%) regressed, including an apparent resolution in 13 (14%) polyps. In 68 (83%) of the 82 polyps at surveillance, histopathology was obtained; 15 (47%) of 32 progressing polyps were advanced adenomas, 6 (21%) of 28 stable polyps, and none of the regressing polyps.

CONCLUSIONS: The majority of 6–9 mm polyps will not progress to advanced neoplasia within 3 years. Those that do progress to advanced status can in particular be found among the lesions that increased in size on surveillance CTC.

December

- Extensive Modulation of the Fecal Metagenome in Children With Crohn's Disease During Exclusive Enteral Nutrition
  - Disease improvement following treatment with EEN is associated with extensive modulation of the gut microbiome.

CJG

- Web of Science
- CJG 2014-2016
- Two papers in top 100
- Editorials

CJG

- Canadian Association of Gastroenterology position statement: Fecal microbiota transplant therapy Moayyedi, Paul, BSc MB ChB PhD MPH FRCP FRCPC ; Marshall, John K, MD MSc FRCPC AGAF ; Yuan, Yuhong, MD PhD ; Hunt, Richard, MB FRCP FRCPC MACG AGAF.

- G Sebastiani, P Ghali, P Wong, MB Klein, M Deschenes, RP Myers. Physicians' practices for diagnosing liver fibrosis in chronic liver diseases: A nationwide, Canadian survey. Can J Gastroenterol Hepatol 2014;28(1):23-30.
  - CONCLUSIONS: Physicians who manage patients with chronic liver diseases in Canada require routine assessment of liver fibrosis stage. Although biopsy remains the primary diagnostic tool for almost one- half of respondents, noninvasive methods, particularly Fibroscan, have significantly reduced the need for liver biopsy in Canada.

Hepatitis C and the sex trade. S Shafran

- Gaps in the hepatitis C continuum of care among sex trade workers in Vancouver, British Columbia: Implications for voluntary hepatitis C virus testing, treatment and care M Eugenia Socías, Kate Shannon PhD, Julio S Montaner, Silvia Guillemi, Sabina Dobrer, Paul Nguyen, Shira Goldenberg, Kathleen Deering

- Conclusions: Despite a high burden of HCV among sex workers, large gaps in the HCV care continuum remain. Particularly concerning are the low access to HCV testing, with one-fifth of women living with HCV being previously unaware of their status, and the exceptionally low prevalence of HCV treatment. There is a critical need for further research to better understand and address barriers to engage in the HCV continuum for sex workers.

IBD: Appreciating disability and impact of disease. S Ghosh

- Living with inflammatory bowel disease: A Crohn's and Colitis Canada survey Helen M Becker, Daniel Grigat, Subrata Ghosh, Gilaad G Kaplan, Levinus Dieleman, Eytan Wine, Richard N Fedorak, Aida Fernandes, Remo Panaccione, Herman W Barkema
- Clinical practice guidelines for the medical management of nonhospitalized ulcerative colitis: the patient perspective A Hillary Steinhart, Aida Fernandes

Genetic testing for hemochromatosis: Diagnostic or confirmatory test for iron overload. Paul Adams

- MB Lanktree, BB Lanktree, G Paré, JS Waye, B Sadikovic, MA Crowther. Examining the clinical use of hemochromatosis genetic testing. Can J Gastroenterol Hepatol 2015;29(1):41-45.
- DISCUSSION: One-half of patients referred for testing did not exhibit biochemical evidence of iron overload. Many patients with biochemical evidence of iron overload, but with negative genetic test results, did not undergo phlebotomy. A requisition to determine clinical indication for testing may reduce the use of the HFE genetic test. Finally, improvement of current genetic test characteristics would improve rationale for the test.
- CONCLUSION: A significant proportion of hemochromatosis genetic testing does not adhere to current guidelines and would not alter patient management.

Should we establish standards of care for management of elderly patients with IBD? Subrata Ghosh

- P Stepaniuk, CN Bernstein, z Nugent, H Singh. Characterization of inflammatory bowel disease in hospitalized elderly patients in a large central Canadian health region. Can J Gastroenterol Hepatol 2015;29(5):274-278.

- RESULTS: One hundred forty-three elderly and 82 young patients with an IBD discharge diagnosis, and 135 elderly patients with other gastrointestinal discharge diagnoses were included. Elderly IBD patients were less likely to have ileocolonic Crohn disease (21.4% versus 50.9%; P=0.001), more likely to be prescribed 5-aminosalicylates (61% versus 43%; P=0.04), and less likely to be prescribed biologics (6% versus 21%; P=0.016) or immunomodulators (21% versus 42%; P=0.01). The sensitivity, specificity and positive predictive value of a single ICD code for CD were 98%, 96% and 94%, respectively, and for ulcerative colitis (UC) were 98%, 92% and 70%, respectively.

- CONCLUSIONS: Treatment approaches in elderly patients were different than in younger IBD patients despite having disease sufficiently severe to require hospitalization. While less accurate in UC, a single ICD-10 IBD code was sufficient to identify elderly CD and UC hospitalized patients.

Summary


AJG
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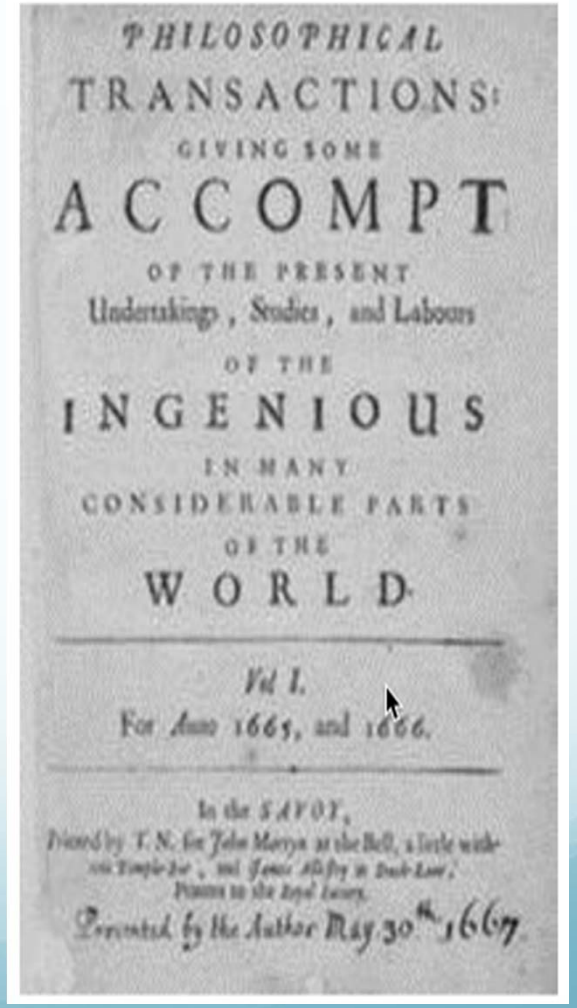
GASTROENTEROLOGY & HEPATOLOGY
pulsus

Take a breath and have a stretch!

- Part 2:
  - Scientific, Technical and Medical Publishers
    - STM Report, 4th Ed, March 2015
    - 350th Anniversary of Journal Publication


PHILOSOPHICAL
TRANSACTIONS:
GIVING SOME
ACCOMPT
OF THE PRESENT
Undertakings, Studies, and Labours
OF THE
INGENIOUS
IN MANY
CONSIDERABLE PARTS
OF THE
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Vol I.
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Temple-Bar, and James Allestry in Duck-Lane,
Printers to the Royal Society.
Presented by the Author May 30th 1667.

Journals in 2015

- Costs, profits, access a big issue
  - But, industry worth $10 billion in 2013 (8 in 2008)
  - USA 28%
  - ~110,000 jobs

- 5000-10000 Journal publishers

Journals 2015

- 2014 – 28,100 Peer Reviewed English Language Journals (likely around 1000 GI related Journals)
- ~2.5 million articles per year
  - Increase by 3-3.5% per year
- 7-9 million researchers- 20% are repeat authors

Question

- If you were to read every English language article published in 2015, how long would it take?
- A) a week
- B) a year
- C) 10 years
- D) 52 years
- E) 104 years

Gut 2015

ORIGINAL ARTICLE

Intergenerational reduction in *Helicobacter pylori* prevalence is similar between different ethnic groups living in a Western city

Wouter J den Hollander,[1,2] I Lisanne Holster,[1] Bianca van Gilst,[1]
Anneke J van Vuuren,[1] Vincent W V Jaddoe,[2,4,5] Albert Hofman,[5]
Guillermo I Perez-Perez,[6] Ernst J Kuipers,[1,3] Henriëtte A Moll,[4] Martin J Blaser[6]

Conclusions Although the highest *H. pylori* and CagA prevalence was found in children of non-Dutch ethnicities, the decreased colonisation rates were uniform across all ethnic groups, implying the importance of environmental factors in *H. pylori* transmission in modern cities, independent of ethnicity.

Significance of this study

What is already known about this subject?

- *Helicobacter pylori* prevalence of children living in Western countries is low.
- Maternal *H. pylori* status is an important transmission source for *H. pylori* colonisation in their children.
- Migrant communities in Western populations constitute risk groups for *H. pylori* colonisation.

What are the new findings?

- A high intergenerational reduction in *H. pylori* prevalence was found, comparing mothers with their children, with nearly identical rates (76% and 77%) for $Hp^{+}CagA^{-}$ and $Hp^{+}CagA^{+}$-strains, respectively.
- The intergenerational drop in *H. pylori* prevalence was uniform in nine separate ethnicities.
- Risk factors for *H. pylori* positivity are mostly the same among diverse ethnic groups.
- Our data suggest a continuing acquisition of *H. pylori* at least till age 7 years.

How might it impact on clinical practice in the foreseeable future?

- The maternal-child linkage is to some degree predictive of *H. pylori* positivity in a child, which affects risk of subsequent diseases.

OPEN ACCESS

ORIGINAL ARTICLE

Improvement over time in outcomes for patients undergoing endoscopic therapy for Barrett's oesophagus-related neoplasia: 6-year experience from the first 500 patients treated in the UK patient registry

R J Haidry,[1,2] M A Butt,[1] J M Dunn,[3,4] A Gupta,[2] G Lipman,[1] H L Smart,[5] P Bhandari,[6] L Smith,[7] R Willert,[8] G Fullarton,[9] M Di Pietro,[10] C Gordon,[11] I Penman,[12] H Barr,[13] P Patel,[14] N Kapoor,[15] J Hoare,[16] R Narayanasamy,[17] Y Ang,[18] A Veitch,[19] K Ragunath,[20] M Novelli,[2] L B Lovat,[1,2] on behalf of the UK RFA Registry

Conclusions Clinical outcomes for BE neoplasia have improved significantly over the past 6 years with improved lesion recognition and aggressive resection of visible lesions before RFA. Despite advances in technique, the rate of cancer progression remains 2–4% at 1 year in these high-risk patients.

Trial registration number ISRCTN93069556.

Significance of this study

What is already known on this subject?

- High-grade dysplasia and intramucosal cancer arising in Barrett's oesophagus (BE) can carry a 40–60% risk of progressing to oesophageal adenocarcinoma.
- The British Society of Gastroenterology has recently released guidelines recommending that patients with BE-related neoplasia and disease confined to the mucosa (T1a) should be offered endoscopic therapy as first-line treatment.
- The radiofrequency ablation (RFA) registry was founded in 2008 to audit and monitor the outcomes of those undergoing minimally invasive endoscopic therapy.

What are the new findings?

- Between 2011 and 2013 there has been a significant improvement in clinical outcomes for patients undergoing endoscopic treatment for BE-related neoplasia.
- Reversal of all dysplasia has risen from 77% to 92% at 12 months compared with patients treated between 2007 and 2010.
- Between 2011 and 2013 the progression to invasive cancer at 12 months was 2.1% and the calculated cancer risk at almost 34 months is 3%.
- Latterly, endoscopic mucosal resection is more widely used prior to initiating RFA, but the risk of symptomatic stenosis requiring endoscopic therapy has not changed over time.

How might it impact on clinical practice in the foreseeable future?

- There is now consensus that first-line treatment for mucosal neoplasia arising in BE should be endoscopic therapy.
- Lesion recognition and resection prior to RFA are paramount to successful outcomes in patients with BE neoplasia. Visible and nodular lesions are more likely to harbour more advanced neoplasia, so early resection is key to both definitive staging and eradication prior to RFA.

Question

- You are consenting a patient with a first degree relative family Hx. of CRC for colonoscopy. You explain that there is a possibility for missing polyps or cancers. What rate would you give?
- A) 2%
- B) 4%
- C) 6%
- D) 8%
- E) Greater than 9%

Gut 2015

Endoscopy

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ORIGINAL ARTICLE

Post-colonoscopy colorectal cancer (PCCRC) rates vary considerably depending on the method used to calculate them: a retrospective observational population-based study of PCCRC in the English National Health Service

Eva J A Morris,[1] Matthew D Rutter,[2,3,4] Paul J Finan,[3,5] James D Thomas,[6] Roland Valori[7]

Conclusions The method used to determine PCCRC rates significantly affects findings with potential to substantially underestimate rates. To enable international benchmarking there needs to be a standardised method for defining PCCRC. This study proposes a new methodology using colonoscopy as a denominator and between 2001 and 2007 this method indicated an 8.6% PCCRC rate across the English NHS. It also demonstrated PCCRC rates have fallen over time.

Significance of this study

What is already known on the topic?

- Post-colonoscopy colorectal cancer (PCCRC) rates have been proposed as a key quality indicator of a colonoscopy service.
- Several methods of calculating PCCRC rates have been published, with reported rates varying between 2.1% and 7.5%.
- Little is known about PCCRC rates in the English National Health Service (NHS).

What are the new findings?

- Rates of PCCRC vary considerably in relation to the method used to define a PCCRC.
- The preferred methodology demonstrated a PCCRC rate within 3 years of colonoscopy of 8.6% in the English NHS.
- PCCRC rates have fallen over time.

How might it impact on clinical practice in the foreseeable future?

- The application of a PCCRC indicator for colonoscopy providers based on routine linked NHS data offers a practical method for assessing the quality of the services delivered.
- For international benchmarking an agreed method for defining PCCRC rate is required.

Commentary

Monitoring postcolonoscopy colorectal cancers: dangerous crossroads?

Silvia Sanduleanu,[1] Catherine Dubé[2]

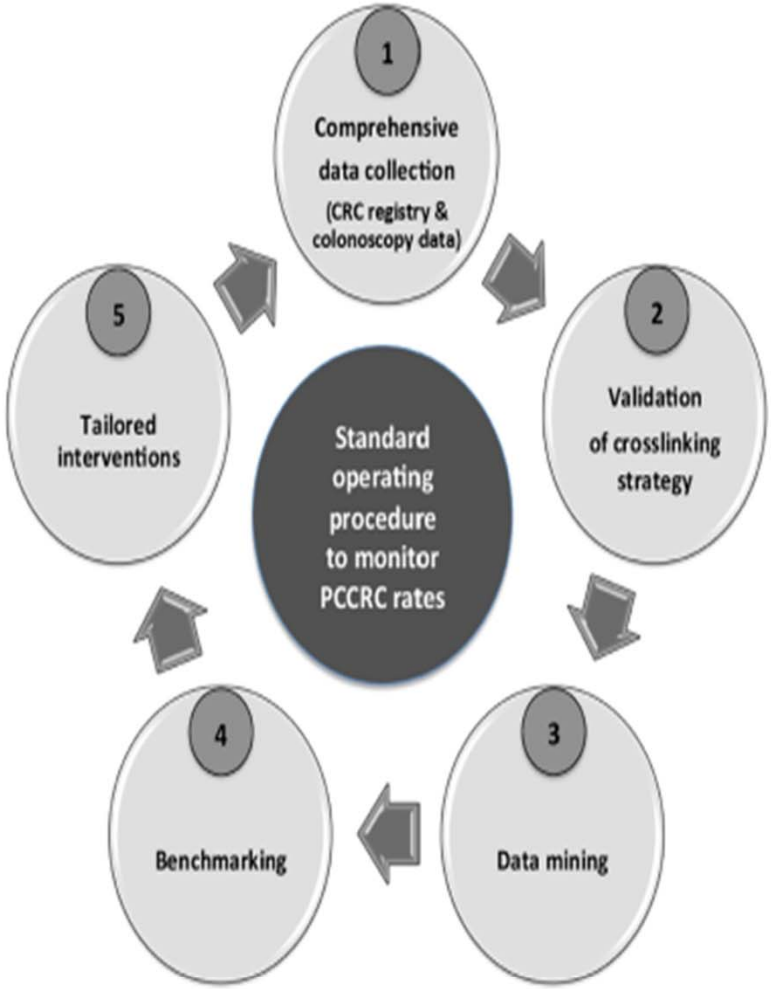

Figure 1 Our proposal for standard operating procedure to monitor postcolonoscopy colorectal cancers (PCCRCs) within and outside screening programmes. The creation of a comprehensive CRC registry that links with colonoscopy data is a crucial first step. In the next phase, the crosslinking strategy needs to be verified and validated through case ascertainment. Data analysis and data mining should then be performed by a multidisciplinary team. Such a structured approach will facilitate benchmarking and tailored interventions.

ORIGINAL ARTICLE

Global patterns of cardia and non-cardia gastric cancer incidence in 2012

A Colquhoun,[1] M Arnold,[2] J Ferlay,[2] K J Goodman,[1] D Forman,[2] I Soerjomataram[2]

Conclusions This study has, for the first time, quantified global incidence patterns of CGC and NCGC providing new insights into the global burden of these cancers. Country-specific estimates are provided; however, these should be interpreted with caution. This work will support future investigations across populations.

Significance of this study

What is already known on this subject?

- Gastric cancer is a major contributor to the global cancer burden, ranking as the fifth most common malignancy worldwide in 2012.
- The two major topographical subsites of gastric cancer, cardia and non-cardia, display distinct characteristics in their descriptive epidemiology and risk factor profiles.
- Cardia and non-cardia gastric cancer incidence rates have been reported for some countries, with cardia rates typically lower than non-cardia rates.

What are the new findings?

- The highest estimated regional age-standardised incidence rates of both gastric cancer subsites occur in Eastern/Southeastern Asia.
- For country-specific estimates, cardia gastric cancer rates were highest in countries within Central Asia; non-cardia rates were highest in countries within Eastern/Southeastern Asia.
- Men had higher estimated rates than women, particularly for cardia gastric cancer.
- For several populations, for example, for men in Australia, the USA and the UK, estimated cardia gastric cancer rates were comparable with or exceeded estimated non-cardia gastric cancer rates.

How might it impact on clinical practice in the foreseeable future?

- This work provides further insights into the global burden of gastric cancer and will aid planning and decision making related to gastric cancer control strategies.

Question

- You see a flat right sided polyp at colonoscopy. What factors could indicate a greater risk for failure of removal?
- A) previous APC use
- B)ICV involvement
- C)behind a fold
- D)all
- E) B & C

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British Society of Gastroenterology/Association of Coloproctologists of Great Britain and Ireland guidelines for the management of large non-pedunculated colorectal polyps

Matthew D Rutter,[1,2] Amit Chattree,[2] Jamie A Barbour,[3] Siwan Thomas-Gibson,[4] Pradeep Bhandari,[5] Brian P Saunders,[4] Andrew M Veitch,[6] John Anderson,[7] Bjorn J Rembacken,[8] Maurice B Loughrey,[9] Rupert Pullan,[10] William V Garrett,[11] Gethin Lewis,[12] Sunil Dolwani[12]

Table 3 Independent risk factors for failed endotherapy[9]

Feature	Statistical association (n=479)
Previous intervention	OR: 3.75; 95% CI 1.77 to 7.94; p=0.001
Ileocaecal valve involvement	OR=3.38; 95% CI 1.20 to 9.52; p=0.021
Difficult position	OR=2.17; 95% CI 1.14 to 4.12; p=0.019
Lesion size >40 mm	OR=4.37; 95% CI 2.43 to 7.88; p<0.001
Previous APC use	OR=3.51; 95% CI 1.69 to 7.27; p=0.001

APC, argon plasma coagulation.

Key questions we sought to cover included:

1. What are the key definitions and terms associated with LNPCPs?
2. What are the available management options?
3. What are the key principles for optimal management, including both assessment and therapy?
4. Which are the most complex lesions and how should they be managed?
5. What histopathological considerations are important in the management of LNPCPs?
6. When is surgical or conservative management more appropriate than endoscopic therapy?
7. Can multidisciplinary input into assessment and therapy improve management?
8. What information should patients be given about their management?
9. How should anticoagulant and antiplatelet drugs be managed before and after procedure?
10. How should patients be followed up after endoscopic removal of LNPCPs?
11. What are the most appropriate key performance indicators for monitoring the quality of management of LNPCPs?
12. What can be done to improve formal training in the management of LNPCPs?
13. What aspects of LNPCP management have the weakest evidence base and what are the key research questions which will help address these?

Table 4 Scoring system to assess polyp difficulty[19]

Parameter	Range	Score
Size	<1 cm	1
	1–1.9 cm	3
	2–2.9 cm	5
	3–3.9 cm	7
	>4 cm	9
Morphology	Pedunculated	1
	Sessile	2
	Flat	3
Site	Left	1
	Right	2
Access	Easy	1
	Difficult	3

Rutter MD, *et al*. *Gut* 2015;**64**:1847–1873. doi:10.1136/gutjnl-2015-309576

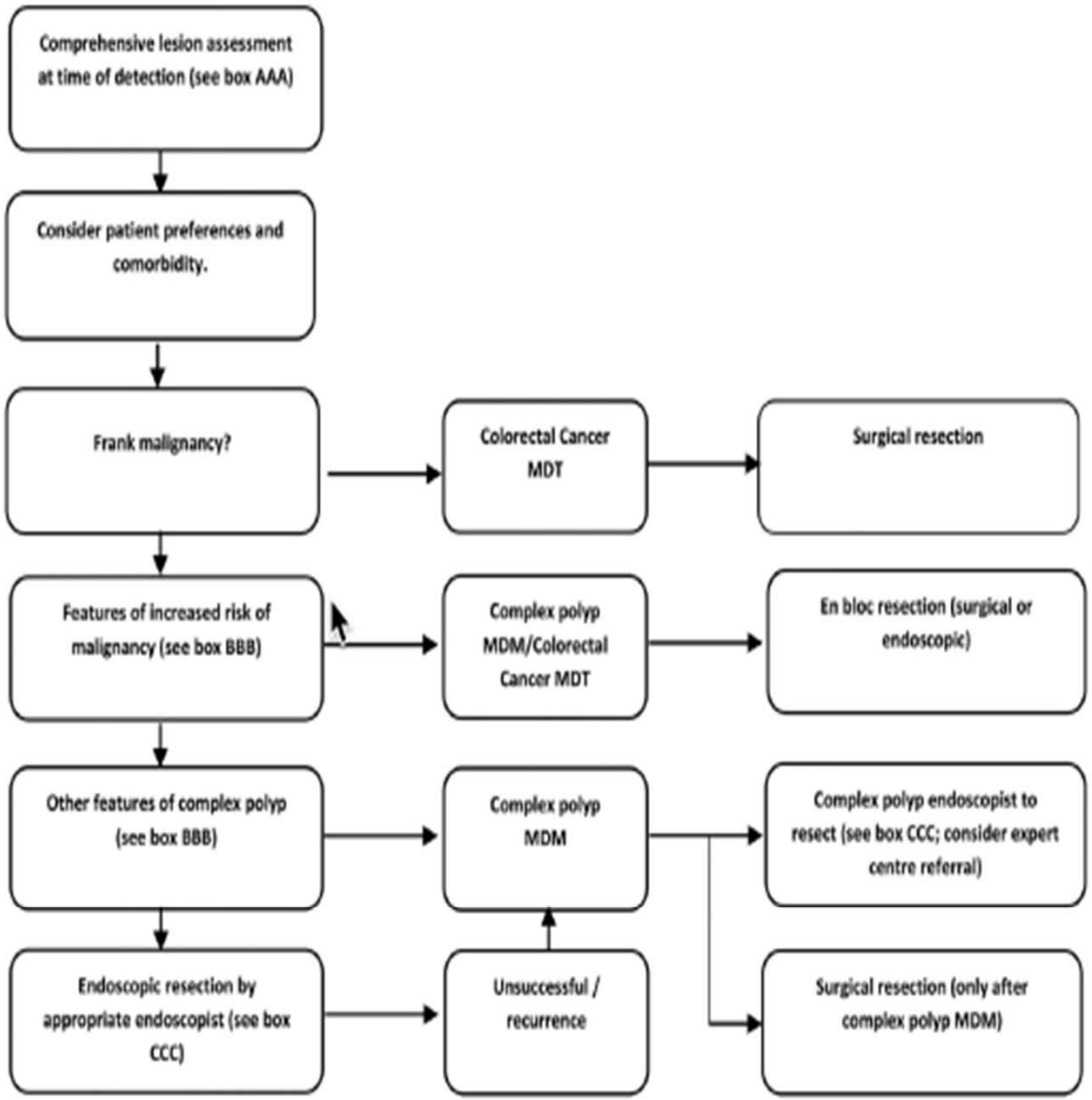


Figure 4 Suggested management algorithm after large non-pedunculated colorectal polyps (LNPCP) identification. Box A (see figure 5); box B (see figure 6); box C (see figure 7). MDM, multidisciplinary meeting; MDT, multidisciplinary team.

- Photograph or video prior to removal
- Estimate size
- Paris Classification (polyp morphology)
- Describe surface characteristics (using e.g. NICE NBI or Kudo Pit Pattern)
- Targeted biopsies only if suspicion of malignancy, caution advised as biopsy may not be necessary for lesions considered benign with a high degree of confidence
- Do not resect at time of discovery (unless consent, time and expertise allow)

Figure 5 Box A: Lesion assessment. NBI, narrow band imaging.

Figure 7 Box C: Endoscopic management. APC, argon plasma coagulation.

Planning
- Adequate planning (time, endoscopist, kit, nurses) to ensure single procedure resection
- Consent (options, risks) with written information in plain English
- Manage antithrombotic medications as per BSG guidelines

Procedure
- Use carbon dioxide
- Use submucosal injection solution with contrast agent and low concentration adrenaline
- Avoid pure cutting or prolonged pure coagulation current
- Piecemeal may be preferable for larger and/or proximal lesions
- Non-lifting lesions should not be subjected to attempted resection by conventional snare polypectomy
- Snare resect a lesion completely wherever possible (APC or soft coagulation only when further snare resection not possible)
- Careful post-procedure inspection of the resection site and photographic documentation
- Tattoo site in accordance with local policy

Post-procedure
- Provide patient with written information about post-procedure complications with recommended actions and an emergency phone number
- Check site 2-6 months after piecemeal endoscopic resection
- Positively identify, photograph & assess scar with image enhancement techniques

ORIGINAL ARTICLE

Identification of inflammatory mediators in patients with Crohn's disease unresponsive to anti-TNFα therapy

Raquel Franco Leal,[1,2] Núria Planell,[1,3] Radhika Kajekar,[4,5] Juan J Lozano,[3] Ingrid Ordás,[1] Isabella Dotti,[1] Miriam Esteller,[1] M Carme Masamunt,[1] Harsukh Parmar,[4,6] Elena Ricart,[1] Julián Panés,[1] Azucena Salas[1]

Conclusions Our results show that anti-TNFα therapy significantly downregulates a subset of inflammatory genes even in patients who fail to achieve endoscopic remission, suggesting that these genes may not be dominant in driving inflammation in non-responders. On the other hand, we identified IL1B and IL17A as genes that remained altered in non-responders, pointing to potentially more relevant targets for modulating mucosal damage in refractory patients.

Significance of this study

What is already known on this subject?

- Anti-tumour necrosis factor α (anti-TNFα) antibodies are effective in managing Crohn's disease and for many patients, provide a therapeutic alternative.
- 40% of patients will not respond to this treatment or will have a loss of response that is not related to immunogenicity.
- The mechanisms sustaining active inflammation in inflammatory bowel disease in the presence of effective TNFα blockade have not been established.

What are the new findings?

- Anti-TNFα therapy regulates a subset of inflammation-dependent genes, including IL6 and IL23p19, regardless of response to treatment.
- Modulation of TNFα-dependent genes in non-responsive patients suggests that lack of a response to anti-TNFα does not result from the absence of biological activity of the administered antibody.
- Patients who are refractory to anti-TNFα therapy maintain deregulated transcription of a set of genes including IL1B, S100A8, S100A9, CXCL2, CXCL6 and S100A12.
- Pathway analysis of TNFα-resistant genes identified IL17A as a potential mediator driving anti-TNFα refractory inflammation.

How might it impact on clinical practice in the foreseeable future?

- Genes that remained altered in patients not responding to TNF blockade (ie, IL1B, IL17A) may be effective targets for inducing remission in this group of patients with refractory disease.
- In contrast, the targeting of mediators, such as IL6, which are downregulated by anti-TNFα treatment even in non-responders, may not provide additional benefits to patients with refractory disease.

OPEN ACCESS

ORIGINAL ARTICLE

Colorectal cancer screening uptake over three biennial invitation rounds in the English bowel cancer screening programme

Siu Hing Lo,[1] Stephen Halloran,[2,3,4] Julia Snowball,[2] Helen Seaman,[2,3,4] Jane Wardle,[1] Christian von Wagner[1]

Conclusions Screening history is associated with overall gFOB uptake, inadequate gFOB screening and follow-up compliance. Socioeconomic deprivation is also consistently associated with lower gFOB uptake and inadequate gFOB screening. Improving regular screening among identified 'at-risk' groups is important for the effectiveness of CRC screening programmes.

Significance of this study

What is already known on this subject?

- There are strong sex and socioeconomic inequalities in colorectal cancer (CRC) screening uptake.
- Screening history is strongly associated with subsequent CRC uptake.
- Repeated invitations to screening successfully engage previous non-responders.
- While many respond to at least one screening invitation over multiple invitation rounds, a considerably smaller number respond consistently to all invitations.

What are the new findings?

- Dropout in the second biennial invitation round following a screen in the first round is associated with lower uptake in the third round than delayed prevalence screening in the second round.
- Socioeconomic inequalities in uptake persist, while sex inequalities decrease over three invitation rounds.
- An irregular screening history and socioeconomic deprivation are associated with inadequate gFOB screening (failing to complete multiple gFOB test kits needed to reach a conclusive test result).
- Screening history is predictive of compliance with follow-up examinations (usually colonoscopy).

How might it impact on clinical practice in the foreseeable future?

- An irregular screening history and socioeconomic deprivation are risk factors of non-compliance at various stages in the CRC screening process.
- Efforts to increase (continued) engagement among these 'at-risk' groups are important to optimise the long-term impact of organised screening programmes.

ORIGINAL ARTICLE

Colon capsule versus CT colonography in patients with incomplete colonoscopy: a prospective, comparative trial

Cristiano Spada,[1] Cesare Hassan,[1] Brunella Barbaro,[2] Franco Iafrate,[3] Paola Cesaro,[1] Lucio Petruzziello,[1] Leonardo Minelli Grazioli,[1] Carlo Senore,[4] Gabriella Brizi,[2] Isabella Costamagna,[1] Giuseppe Alvaro,[2] Marcella Iannitti,[3] Marco Salsano,[2] Maria Ciolina,[3] Andrea Laghi,[3] Lorenzo Bonomo,[2] Guido Costamagna[1]

Conclusions CCE and CTC were of comparable efficacy in completing colon evaluation after incomplete colonoscopy; the overall diagnostic yield of colon capsule was superior to CTC.

Significance of this study

What is already known on this subject?

- Colonoscopy may be incomplete in 4–15% of patients.
- CT colonography (CTC) is the imaging modality of choice in case of incomplete colonoscopy.
- Preliminary data suggest that colon capsule endoscopy (CCE) is a feasible and safe tool for colon mucosa visualisation in patients with incomplete colonoscopy without stenosis.
- Studies comparing CCE with radiological imaging, and in particular with CTC, are lacking.

What are the new findings?

- CCE and CTC are very effective in completing incomplete colonoscopy.
- CCE diagnostic yield is superior to that of CTC, when using colonoscopy for positive cases as gold standard.
- The superiority of CCE appears mainly to be related with a higher accuracy for 6–9 mm and/or non-polypoid lesions.

How might it impact on clinical practice in the foreseeable future?

- Where CCE is available, it may be considered among the first-choice tests in case of incomplete colonoscopy.
- Incomplete colonoscopy might be considered an appropriate indication for CCE.

ORIGINAL ARTICLE

Risk of irritable bowel syndrome in first-degree, second-degree and thirddegree relatives of affected individuals: a nationwide family study in Sweden

Rasmus Waehrens,[1] Henrik Ohlsson,[1] Jan Sundquist,[1,2] Kristina Sundquist,[1,2] Bengt Zöller[1]

Conclusions The increased IBS risk among first-degree relatives and also second-degree and third-degree relatives indicates a genetic component of the familial clustering of IBS. However, a non-genetic contribution is also suggested by the increased risk among spouses.

Significance of this study

What is already known on this subject?

- IBS is known to aggregate in families.
- Familial aggregation may be due to shared genetic or environmental factors.

What are the new findings?

- IBS aggregates in Swedish families, and a non-genetic familial contribution is suggested by the increased risk among spouses.
- A genetic contribution to the familial aggregation of IBS in Sweden is suggested by the increased familial risks among first-degree relatives and also second-degree and third-degree relatives.
- This the largest register-based family study of IBS, and the first nationwide one.

How might it impact on clinical practice in the foreseeable future?

- Family history of IBS is a potential useful predictor for IBS.
- Genetic studies in order to identify IBS-associated genetic variants might be worthwhile.

ORIGINAL ARTICLE

Oesophageal adenocarcinoma and prior diagnosis of Barrett's oesophagus: a population-based study

Shivaram K Bhat,[1] Damian T McManus,[2] Helen G Coleman,[1] Brian T Johnston,[3] Christopher R Cardwell,[1] Úna McMenamin,[1] Finian Bannon,[4] Blanaid Hicks,[1] Grace Kennedy,[1] Anna T Gavin,[4] Liam J Murray[1]

Conclusions The proportion of OAC patients with a prior diagnosis of BO is low; however, prior identification of BO is associated with an improvement in survival in OAC patients.

Significance of this study

What is already known on this subject?

- Endoscopic surveillance of Barrett's oesophagus is widely practised in an effort to improve outcomes from oesophageal adenocarcinoma.
- The impact of surveillance on population outcomes from oesophageal adenocarcinoma will depend on the proportion of patients that had previously been diagnosed with Barrett's oesophagus.
- The improved outcomes associated with surveillance may in part be due to lead and length time bias

What are the new findings?

- The proportion of oesophageal adenocarcinoma patients with previously diagnosed Barrett's oesophagus is low.
- Oesophageal adenocarcinoma patients with a prior Barrett's oesophagus diagnosis were diagnosed with earlier stage disease and had improved survival compared with adenocarcinoma patients with no prior Barrett's oesophagus diagnosis.
- The improved survival observed in patients with a prior diagnosis of Barrett's oesophagus remained after correction for lead and length time biases of plausible magnitude.

How might it impact on clinical practice in the foreseeable future?

- The low proportion of patients with a prior Barrett's oesophagus diagnosis suggests that endoscopic surveillance of Barrett's oesophagus, as currently practised, can only have a modest impact on population oesophageal adenocarcinoma outcomes.
- Better methods of identifying patients in the population at greatest risk of developing oesophageal adenocarcinoma are required in order to allow targeted surveillance and improve population outcomes from oesophageal adenocarcinoma.

ORIGINAL ARTICLE

An updated Asia Pacific Consensus Recommendations on colorectal cancer screening

J J Y Sung,[1] S C Ng,[1,2] F K L Chan,[1,2] H M Chiu,[3] H S Kim,[4] T Matsuda,[5] S S M Ng,[6] J Y W Lau,[6] S Zheng,[7] S Adler,[8] N Reddy,[9] K G Yeoh,[10] K K F Tsoi,[11] J Y L Ching,[2] E J Kuipers,[12] L Rabeneck,[13] G P Young,[14] R J Steele,[15] D Lieberman,[16] K L Goh[17]

Conclusions Based on recent data on CRC screening, an updated list of recommendations on CRC screening is prepared. These consensus statements will further enhance the implementation of CRC screening in the Asia Pacific region.

Significance of this study

What is already known on this subject?
In previous Asia Pacific consensus recommendations:

- Consensus on Colorectal Cancer (CRC) screening should be started at the age of 50 years.
- Faecal immunochemical test (FIT), guaiac-based faecal occult blood test (gFOBT), flexible sigmoidoscopy and colonoscopy are recommended for CRC screening.
- FOBT is the first choice for CRC screening in resource-limited countries.

What are the new findings?
In this updated Asia Pacific consensus recommendations:

- Age range for CRC screening is defined as 50–75 years.
- A risk-stratified scoring system is recommended to select high-risk patients for early colonoscopy.
- Quantitative FIT, but not gFOBT, is preferred for average-risk subjects.
- Quality control measures should be included in CRC screening programmes.

How might it impact on clinical practice in the foreseeable future?

- The Asia Pacific Colorectal Cancer Working Group believes that these consensus statements will further enhance the implementation of CRC screening in the region. It may also be relevant to CRC screening programme in other geographic locations with resource constraints.

Does a prior diagnosis of Barrett's oesophagus influence risk of dying from oesophageal adenocarcinoma?

David C Whiteman

ORIGINAL ARTICLE

Global prevalence of, and risk factors for, uninvestigated dyspepsia: a meta-analysis

Alexander C Ford,[1,2] Avantika Marwaha,[3] Ruchit Sood,[1,2] Paul Moayyedi[3]

Conclusions The overall pooled prevalence of uninvestigated dyspepsia was 21%, but varied among countries and according to the criteria used to define its presence. Prevalence is significantly higher in women, smokers, NSAID users and *H. pylori*-positive individuals, although these associations were modest.

Significance of this study

What is already known on this subject?

- Uninvestigated dyspepsia is common in the community.
- Proposed risk factors include female gender, smoking, non-steroidal inflammatory drug use and *Helicobacter pylori* infection.
- There has been no systematic synthesis of data concerning the prevalence of uninvestigated dyspepsia worldwide.

What are the new findings?

- Up to one in five individuals report dyspepsia in the community.
- Prevalence varies remarkably worldwide, and this is not explained by differing criteria used to define dyspepsia.
- Female gender, smoking, non-steroidal inflammatory drug use and *H. pylori* were only modestly associated with presence of uninvestigated dyspepsia in the community.

How might it impact on clinical practice in the foreseeable future?

- These data provide a robust analysis of the prevalence of uninvestigated dyspepsia, allowing for health service provision planning.
- They could be plotted against other prevalence data, at individual country level, in order to determine novel risk factors for the condition.

Environment and invironment in IBDs: partners in crime

Peter Laszlo Lakatos,[1] Johan Burisch[2]

ORIGINAL ARTICLE

Environmental risk factors in inflammatory bowel disease: a population-based case-control study in Asia-Pacific

Siew C Ng,[1] Whitney Tang,[1] Rupert W Leong,[2] Minhu Chen,[3] Yanna Ko,[2] Corrie Studd,[4] Ola Niewiadomski,[4] Sally Bell,[4] Michael A Kamm,[4,5] H J de Silva,[6] Anuradhani Kasturiratne,[6] Yasith Udara Senanayake,[6] Choon Jin Ooi,[7] Khoon-Lin Ling,[7] David Ong,[8] Khean Lee Goh,[9] Ida Hilmi,[9] Qin Ouyang,[10] Yu-Fang Wang,[10] PinJin Hu,[3] Zhenhua Zhu,[3] Zhirong Zeng,[3] Kaichun Wu,[11] Xin Wang,[11] Bing Xia,[12] Jin Li,[12] Pises Pisespongsa,[13] Sathaporn Manatsathit,[14] Satimai Aniwan,[15] Marcellus Simadibrata,[16] Murdani Abdullah,[16] Steve W C Tsang,[17] Tai Chiu Wong,[18] Aric J Hui,[19] Chung Mo Chow,[20] Hon Ho Yu,[21] Mo Fong Li,[21] Ka Kei Ng,[22] Jessica Ching,[1] Justin C Y Wu,[1] Francis K L Chan,[1] Joseph J Y Sung,[1] on behalf of the Asia-Pacific Crohn's and Colitis Epidemiology Study (ACCESS) Group

Conclusions This first population-based study of IBD risk factors in Asia-Pacific supports the importance of childhood immunological, hygiene and dietary factors in the development of IBD, suggesting that markers of altered intestinal microbiota may modulate risk of IBD later in life.

Significance of this study

What is already known on this subject?

- The rapid increase in IBD incidence supports the influence of environmental factors.
- Smoking has been consistently shown to be a risk factor for Crohn's disease (CD) and a protective factor for UC.
- Limited epidemiological data suggest a link between having been breast fed and risk of developing IBD.

What are the new findings?

- Breast feeding has a marked protective effect on development of CD and UC; the beneficial effect was most prominent when breast feeding was continued for 12 months or longer.
- A more 'Westernised' diet is a risk factor whereas tea/coffee consumption is a protective factor for IBD.
- Contact with childhood pets is a novel protective factor.
- Inverse association between antibiotic use and development of CD suggests that antibiotics may not be a contributing factor to the rising incidence in Asia.

ORIGINAL ARTICLE

Surveillance in patients with long-segment Barrett's oesophagus: a cost-effectiveness analysis

F Kastelein,[1] S van Olphen,[1,2] E W Steyerberg,[3] M Sikkema,[1,4] M C W Spaander,[1] C W N Looman,[3] E J Kuipers,[1] P D Siersema,[1,4] M J Bruno,[1] E W de Bekker-Grob,[3] on behalf of the ProBar-study group

Conclusions Based on a Dutch healthcare perspective and assuming a willingness-to-pay threshold of €35.000 per QALY, surveillance with EMR and RFA for HGD or early OAC, and oesophagectomy for advanced OAC is cost-effective every 5 years for ND and every 3 years for LGD.

Significance of this study

What is already known on this subject?

- Endoscopic surveillance is recommended for Barrett's oesophagus to detect oesophageal adenocarcinoma at an early stage.
- Over the past years, there has been a major shift in the treatment of patients with high-grade dysplasia and oesophageal adenocarcinoma.
- Previous studies have investigated the cost-effectiveness of different surveillance intervals and treatment strategies with conflicting results.

What are the new findings?

- Endoscopic treatment with endoscopic mucosal resection and radiofrequency ablation is a cost-effective alternative for oesophagectomy in patients with high-grade dysplasia or early adenocarcinoma.
- Surveillance every 5 years with endoscopic mucosal resection for high-grade dysplasia or early adenocarcinoma, radiofrequency ablation for residual Barrett's oesophagus and oesophagectomy with neoadjuvant chemoradiotherapy for advanced adenocarcinoma is cost-effective for patients without dysplasia in long-segment Barrett's oesophagus.
- Surveillance every 3 years with endoscopic mucosal resection for high-grade dysplasia or early adenocarcinoma, radiofrequency ablation for residual Barrett's oesophagus and oesophagectomy with neoadjuvant chemoradiotherapy for advanced adenocarcinoma is cost-effective for patients with low-grade dysplasia in long-segment Barrett's oesophagus.

How might it impact on clinical practice in the foreseeable future?

- Surveillance intervals should be prolonged to 5 years for patients without dysplasia and 3 years for patients with low-grade dysplasia in long-segment Barrett's oesophagus in order to be cost-effective.
- Identification of new risk factors is needed to improve risk stratification and thereby the cost-effectiveness of surveillance with shorter surveillance intervals.

ORIGINAL ARTICLE

Global incidence of oesophageal cancer by histological subtype in 2012

Melina Arnold, Isabelle Soerjomataram, Jacques Ferlay, David Forman

Conclusions These first global estimates of oesophageal cancer incidence by histology suggested a high concentration of AC in high-income countries with men being at much greater risk. This quantification of incidence will aid health policy makers to plan appropriate cancer control measures in the future.

Significance of this study

What is already known on this subject?

- The two main types of oesophageal cancer, squamous cell carcinoma (SCC) and adenocarcinoma (AC), differ greatly in their aetiology and epidemiology. To date, however, no global incidence estimates exist.
- While the incidence of AC has been increasing in several high-income countries during the past years, trends in SCC have remained stable or have decreased.

What are the new findings?

- In this study, we quantified for the first time the global burden oesophageal cancer by histological type. In 2012, an estimated 398 000 cases of SCC and 52 000 cases of occurred globally.
- The incidence of SCC was highest in South-Eastern and Central Asia, where 79% of all SCC cases occurred. In contrast, the burden of AC was highest in Northern and Western Europe, Northern America and Oceania, which accounted for 46% of the global AC cases.
- While SCC is the more common type of oesophageal cancer on the global scale, incidence rates of AC notably exceeded those of SCC in the Netherlands and in the UK. This was also true for New Zealand, the USA, Canada, Ireland, Iceland, Australia, Norway, Malta, Sweden, Bahrain and Cyprus.
- For both sites, men had substantially higher incidence than women. This was more pronounced for AC, where incidence in men was on average four times greater than in women and over eight times greater in Northern America.

How might it impact on clinical practice in the foreseeable future?

- This quantification of incidence accords with aetiological research and will aid health policy makers to plan appropriate cancer control measures in the future.

ORIGINAL ARTICLE

Impact on colorectal cancer mortality of screening programmes based on the faecal immunochemical test

Manuel Zorzi,[1] Ugo Fedeli,[2] Elena Schievano,[2] Emanuela Bovo,[1] Stefano Guzzinati,[1] Susanna Baracco,[1] Chiara Fedato,[1] Mario Saugo,[2] Angelo Paolo Dei Tos[1,3]

Conclusions FIT-based screening programmes were associated with a significant reduction in CRC mortality. This effect took place much earlier than reported by gFOBT-based trials and observational studies.

Significance of this study

What is already known on this subject?

- Colorectal cancer (CRC) screening programmes based on the guaiac faecal occult blood test (gFOBT) reduce CRC-specific mortality.
- Several studies have shown higher clinical sensitivity of the faecal immunochemical test (FIT) compared with the gFOBT.
- Data on the impact on mortality of FIT-based screening programmes are still lacking.

What the new findings?

- Areas where FIT screening programmes were active showed a 22% reduction in CRC-specific mortality.
- The impact of FIT programmes on mortality was greater and took place earlier compared with available evidence on gFOBT-based screening programmes.

How might it impact on clinical practice in the foreseeable future?

- A screening schedule based on a single FIT with a positivity cut-off for a haemoglobin concentration of 20 μg Hb/g faeces (100 ng Hb/mL buffer) and an inter-screening interval of 2 years significantly reduces CRC mortality.
- The reduction of incidence rates associated with the removal of precancerous lesions may convey an even higher impact on mortality in the medium–long-term.

ORIGINAL ARTICLE

Bismuth, lansoprazole, amoxicillin and metronidazole or clarithromycin as first-line *Helicobacter pylori* therapy

Wei Zhang,[1,2] Qi Chen,[1,2] Xiao Liang,[1,2] Wenzhong Liu,[1,2] Shudong Xiao,[1,2] David Y Graham,[3] Hong Lu[1,2]

Conclusions These results suggest that amoxicillin can substitute for tetracycline in modified 14 day bismuth quadruple therapy as first-line treatment and still overcome metronidazole resistance in areas with high prevalence of metronidazole and clarithromycin resistance. Using clarithromycin instead of metronidazole was only effective in the presence of susceptible strains.

Significance of this study

What is already known on this subject?

- *Helicobacter pylori* therapies including standard triple therapy no longer reliably achieve acceptable *H. pylori* eradication rates because of increasing antimicrobial resistance.
- Metronidazole resistance can be overcome with traditional bismuth quadruple therapy when given at full dose for 14 days.
- Bismuth quadruple therapy has long been used successfully; it has never become widely used in part because of the relatively high incidence of side effects and because in recent years tetracycline has been largely unavailable.
- Studies without concomitant susceptibility testing may result in misleading conclusions.

What are the new findings?

- Amoxicillin can substitute for tetracycline in bismuth quadruple therapy and still overcome metronidazole resistance (eg, cure rates were 96.4% vs 93.3%) for metronidazole susceptible versus resistant infections.
- A high overall cure rate with the proton pump inhibitor, bismuth, amoxicillin and clarithromycin combination did not reflect an improved cure rate with clarithromycin-resistant strains (eg, 98.6% vs 76.9% for clarithromycin susceptible vs resistant infections).

How might it impact on clinical practice in the foreseeable future?

- This 14-day non-tetracycline-containing bismuth quadruple therapy in which amoxicillin replaced tetracycline is the first new regimen in decades that was able to overcome resistance to a key ingredient (ie, metronidazole) and is thus potentially a new first-line therapy.

Guidelines

OPEN ACCESS

UK guidelines on the management of variceal haemorrhage in cirrhotic patients

Dhiraj Tripathi,[1] Adrian J Stanley,[2] Peter C Hayes,[3] David Patch,[4] Charles Millson,[5] Homoyon Mehrzad,[6] Andrew Austin,[7] James W Ferguson,[1] Simon P Olliff,[6] Mark Hudson,[8] John M Christie[9]

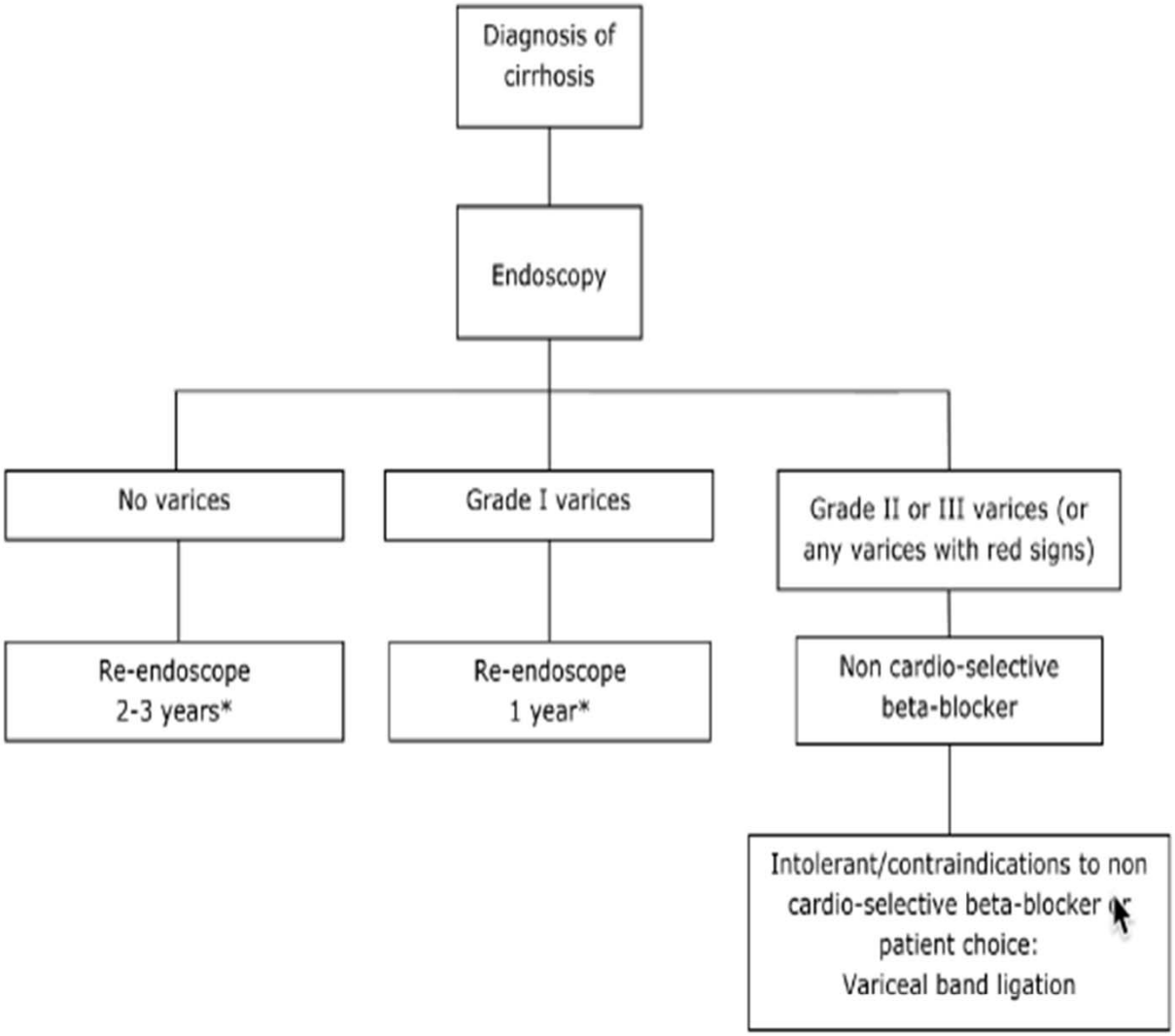
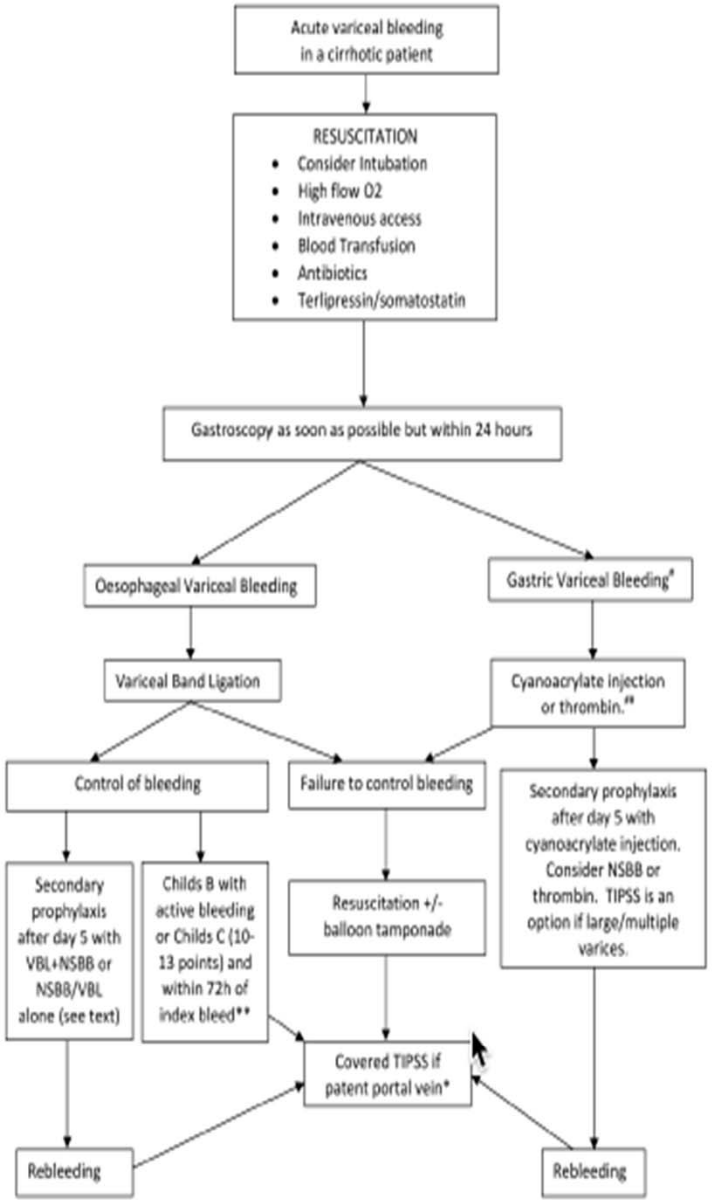


Figure 2 Algorithm for surveillance of varices and primary prophylaxis in cirrhosis.
*– If there is clear evidence of disease progression this interval can be modified by clinician. Endoscopy should also be offered at time of decompensation.

Tripathi D, *et al*. *Gut* 2015;**64**:1680–1704. doi:10.1136/gutjnl-2015-309262

Figure 3 Algorithm for the management of acute variceal bleeding. TIPSS, transjugular intrahepatic portosystemic stent shunt.



ORIGINAL ARTICLE

Effects of bowel cleansing on the intestinal microbiota

Jonna Jalanka,[1] Anne Salonen,[2] Jarkko Salojärvi,[1] Jarmo Ritari,[1] Outi Immonen,[1] Luca Marciani,[3] Penny Gowland,[4] Caroline Hoad,[4] Klara Garsed,[3] Ching Lam,[3] Airi Palva,[1] Robin C Spiller,[3] Willem M de Vos[1,2,5]

Conclusions Our results suggest that the bowel cleansing using two separate dosages introduces fewer alterations to the intestinal microbiota than a single dose and hence may be preferred in clinical practice.

Significance of this study

What is already known on this subject?

- Changes in the intestinal microbiota following bowel cleansing have been detected. However, a detailed description or the long-term effects to the microbiota has not been characterised.
- Two different dosing methods are used in the clinical practice. The effect of the dosing to the intestinal microbiota has not been addressed.
- Faecal serine proteases are predominantly of pancreatic origin and shown to be increased in IBS patients with diarrhoea and after bowel cleansing.

What are the new findings?

- The majority of the intestinal microbiota recovered to the baseline composition after bowel preparation.
- Subjects consuming a single dose (2 L) of the purgative showed increased abundance of several taxa including Proteobacteria and bacteria related to *Dorea formicigenerans* in the follow-up samples and less efficient microbial recovery than the subjects given two separate 1 L dosages.

How might it impact on clinical practice in the foreseeable future?

- These data provide insight into the microbiota changes associated with purgative lavage and may help in the understanding of the changes seen in IBS and other diarrhoeal diseases.
- Two separate dosages of purgative introduced fewer alterations to the intestinal microbiota and resulted in a colon with a lower bacterial load than the single dose.

Commentary

Bowel preparation for colonoscopy: relevant for the gut's microbiota?

Volker Mai,[1] O Colin Stine[2]

OPEN ACCESS

ORIGINAL ARTICLE

The relationship between infliximab concentrations, antibodies to infliximab and disease activity in Crohn's disease

Niels Vande Casteele,[1,2,3] Reena Khanna,[3] Barrett G Levesque,[2,3] Larry Stitt,[3] G Y Zou,[3] Sharat Singh,[4] Steve Lockton,[4] Scott Hauenstein,[4] Linda Ohrmund,[4] Gordon R Greenberg,[5] Paul J Rutgeerts,[6] Ann Gils,[1] William J Sandborn,[2] Séverine Vermeire,[6] Brian G Feagan[3]

Significance of this study

ORIGINAL ARTICLE

Quality of colonoscopy in an organised colorectal cancer screening programme with immunochemical faecal occult blood test: the EQuIPE study (Evaluating Quality Indicators of the Performance of Endoscopy)

Manuel Zorzi,[1] Carlo Senore,[2] Filippo Da Re,[3] Alessandra Barca,[4] Luigina Ada Bonelli,[5] Renato Cannizzaro,[6] Renato Fasoli,[7] Lucia Di Furia,[8] Emilio Di Giulio,[9] Paola Mantellini,[10] Carlo Naldoni,[11] Romano Sassatelli,[12] Douglas Rex,[13] Cesare Hassan,[14] Marco Zappa,[15] the Equipe Working Group

Conclusions The quality of colonoscopy was affected by patient-related, endoscopist-related and centre-related characteristics. Policies addressing organisational issues should improve the quality of colonoscopy in our programme and similar programmes.

Significance of this study

What is already known on this subject?

- Organised colorectal cancer screening programmes with immunochemical faecal test have been implemented in Europe.
- The quality of colonoscopy is critical for the overall success of these organised programmes.
- Adenoma detection rate and caecal intubation rate are the most important indicators of the quality of colonoscopy.

What are the new findings?

- In the Italian screening programme with immunochemical faecal test, the overall level of quality of colonoscopy was adequate, with the adenoma detection and caecal intubation rates being 45% and 93%, respectively.
- There was substantial variation among the endoscopists in both indicators. This variation was explained by at least three levels of predictors, namely at *per-patient*, *per-endoscopist* and *per-centre* levels.
- Gastroenterology specialty, sedation and the availability of screening-dedicated sessions were associated with the adenoma detection rate. Sedation, the availability of screening-dedicated sessions and the volume of screening colonoscopies were associated with the caecal intubation rate.

How might it impact on clinical practice in the foreseeable future?

- Policies addressing organisational issues, such as sedation, the availability of screening sessions and endoscopist retraining are likely to improve the overall quality of colonoscopy in this setting.

ORIGINAL ARTICLE

Value of endoscopy and MRI for predicting intestinal surgery in patients with Crohn's disease in the era of biologics

A Jauregui-Amezaga,[1] J Rimola,[2] I Ordás,[1] S Rodríguez,[2] A Ramírez-Morros,[1] M Gallego,[1] M C Masamunt,[1] J Llach,[1] B González-Suárez,[1] E Ricart,[1] J Panés[1]

Conclusions Perianal disease, stenosis and/or intra-abdominal fistulae at MRI independently predict an increased risk of resection surgery in patients with CD, whereas immunosuppressants and/or anti-TNF therapy reduce such risk. Under current therapeutic strategies, the presence of SELs is not a predictor of resection surgery in patients with CD.

Significance of this study

What is already known on this subject?

- Severe endoscopic colonic lesions in patients with Crohn's disease (CD) have been associated with higher requirements for surgical resection.
- Optimal use of therapeutic options may reduce the risk of surgical resection in patients with CD.

What are the new findings?

- The future need for surgery in patients with CD is best established by a combined clinical and MRI assessment, taking into account the presence of perianal disease, and the presence of stricturing and fistulising lesions.
- Patients receiving immunomodulators and/or antitumor necrosis factor therapy have a lower risk of surgery, independently of the presence of other prior factors.
- Under current therapeutic algorithms, the presence of endoscopic ulcerations is not a predictor of the need for surgery.

How might it impact on clinical practice in the foreseeable future?

- These findings should be taken into account when making therapeutic decisions for patients with CD.

OPEN ACCESS

Kyoto global consensus report on *Helicobacter pylori* gastritis

Kentaro Sugano,[1] Jan Tack,[2] Ernst J Kuipers,[3] David Y Graham,[4] Emad M El-Omar,[5] Soichiro Miura,[6] Ken Haruma,[7] Masahiro Asaka,[8] Naomi Uemura,[9] Peter Malfertheiner,[10] on behalf of faculty members of Kyoto Global Consensus Conference

Conclusions A global consensus for gastritis was developed for the first time, which will be the basis for an international classification system and for further research on the subject.

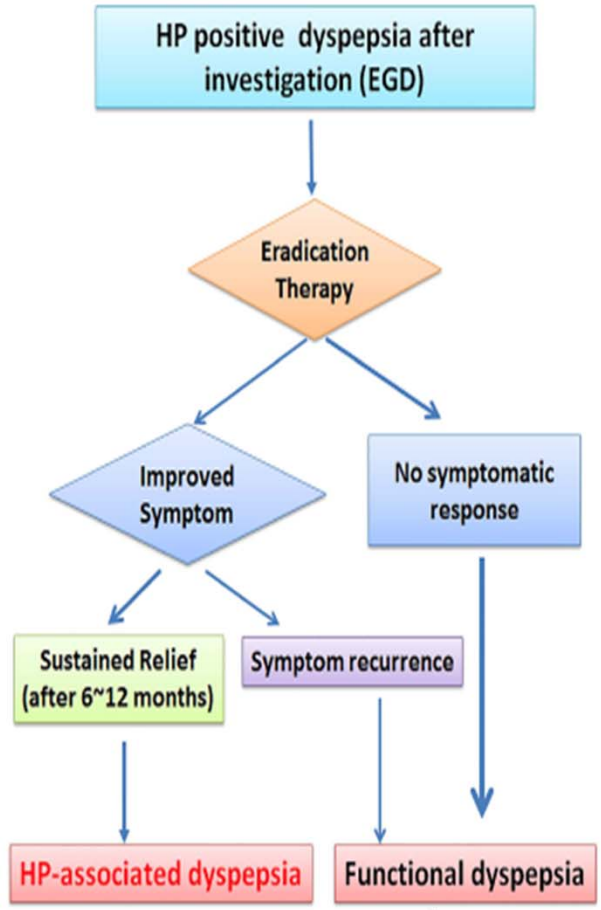


Figure 1 Diagnostic algorithm of *Helicobacter pylori*-associated dyspepsia. Patients with dyspeptic symptoms after negative routine laboratory and upper gastrointestinal endoscopy except for positive *H. pylori* tests, should undergo eradication therapy. If sustained symptomatic relief is obtained, their dyspeptic symptoms are considered as *H. pylori*-associated dyspepsia. On the other hand, if dyspeptic symptoms do not resolve or recur after eradication therapy, they are judged to have functional dyspepsia. EGD, oesophagastroduodenoscopy.

Sugano K, *et al*. *Gut* 2015;**64**:1353–1367. doi:10.1136/gutjnl-2015-309252

Gastroenterology 2015

Gastroenterology 2015;148:719–731

REVIEWS IN BASIC AND CLINICAL GASTROENTEROLOGY AND HEPATOLOGY

Robert F. Schwabe and John W. Wiley, Section Editors

Helicobacter pylori Update: Gastric Cancer, Reliable Therapy, and Possible Benefits

David Y. Graham

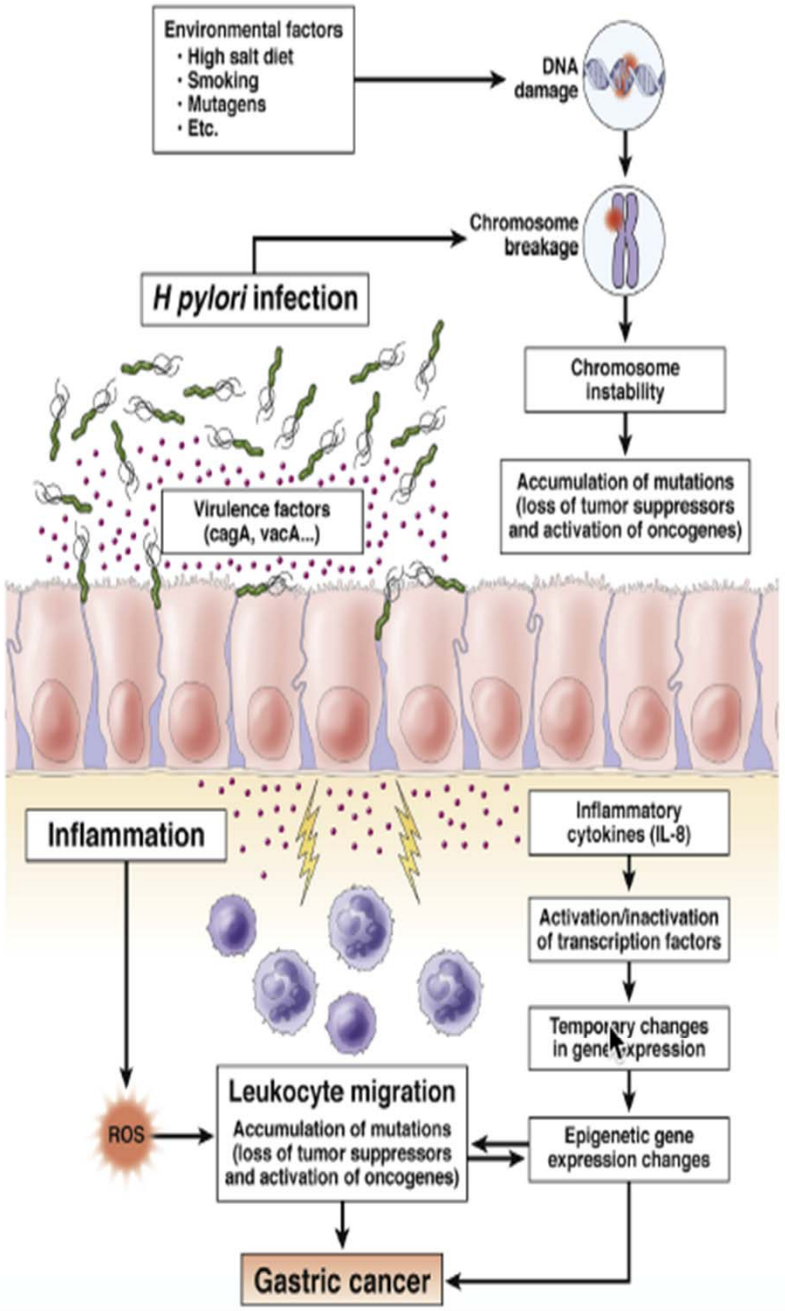


Figure 2. Interactions among inflammation, bacteria, and the epithelium leading to gastric cancer. We show the interaction of *H pylori*, environmental factors, and inflammation in the pathogenesis of gastric cancer. Each plays important roles leading to progressive chromosome instability. *H pylori*–induced inflammation leads to high gastric endothelial cell turnover and a microenvironment that is high in reactive oxygen and nitrogen species, increasing opportunities for DNA damage and somatic mutations. IL, interleukin; ROS, reactive oxygen species. Adapted from Hanada and Graham[3] and Chang et al.[28]

Gastroenterology 2015

Gastroenterology 2015;148:740–750

Budesonide Foam Induces Remission in Patients With Mild to Moderate Ulcerative Proctitis and Ulcerative Proctosigmoiditis

William J. Sandborn,[1] Brian Bosworth,[2] Salam Zakko,[3] Glenn L. Gordon,[4] David R. Clemmons,[5] Pamela L. Golden,[6] Robert L. Rolleri,[6] Jing Yu,[6] Andrew C. Barrett,[6] Enoch Bortey,[6] Craig Paterson,[6] and William P. Forbes[6]

[1]Division of Gastroenterology, University of California–San Diego, La Jolla, California; [2]New York-Presbyterian Hospital/Weill Cornell Medical Center, New York, New York; [3]Connecticut Gastroenterology Institute, Bristol, Connecticut; [4]Center for Digestive and Liver Diseases, Inc, Mexico, Missouri; [5]University of North Carolina School of Medicine, Chapel Hill, North Carolina; and [6]Salix Pharmaceuticals, Inc, Raleigh, North Carolina

BACKGROUND & AIMS: Budesonide is a high-potency, second-generation corticosteroid designed to minimize systemic adverse consequences of conventional corticosteroids. We performed 2 randomized, phase 3 trials to evaluate the ability of budesonide rectal foam, formulated to optimize retention and provide uniform delivery of budesonide to the rectum and distal colon, to induce remission in patients with ulcerative proctitis or ulcerative proctosigmoiditis. **METHODS:** Two identically designed, randomized, double-blind, placebo-controlled trials evaluated the efficacy of budesonide foam for induction of remission in 546 patients with mild to moderate ulcerative proctitis or ulcerative proctosigmoiditis who received budesonide foam 2 mg/25 mL twice daily for 2 weeks, then once daily for 4 weeks, or placebo. **RESULTS:** Remission at week 6 occurred significantly more frequently among patients receiving budesonide foam than placebo (Study 1: 38.3% vs 25.8%; $P = .0324$; Study 2: 44.0% vs 22.4%; $P < .0001$). A significantly greater percentage of patients receiving budesonide foam vs placebo achieved rectal bleeding resolution (Study 1: 46.6% vs 28.0%; $P = .0022$; Study 2: 50.0% vs 28.6%; $P = .0002$) and endoscopic improvement (Study 1: 55.6% vs 43.2%; $P = .0486$; Study 2: 56.0% vs 36.7%; $P = .0013$) at week 6. Most adverse events occurred at similar frequencies between groups, although events related to changes in cortisol values were reported more frequently with budesonide foam. There were no cases of clinically symptomatic adrenal insufficiency. **CONCLUSIONS:** Budesonide rectal foam was well tolerated and more efficacious than placebo in inducing remission in patients with mild to moderate ulcerative proctitis and ulcerative proctosigmoiditis. ClinicalTrials.gov ID: NCT01008410 and NCT01008423.

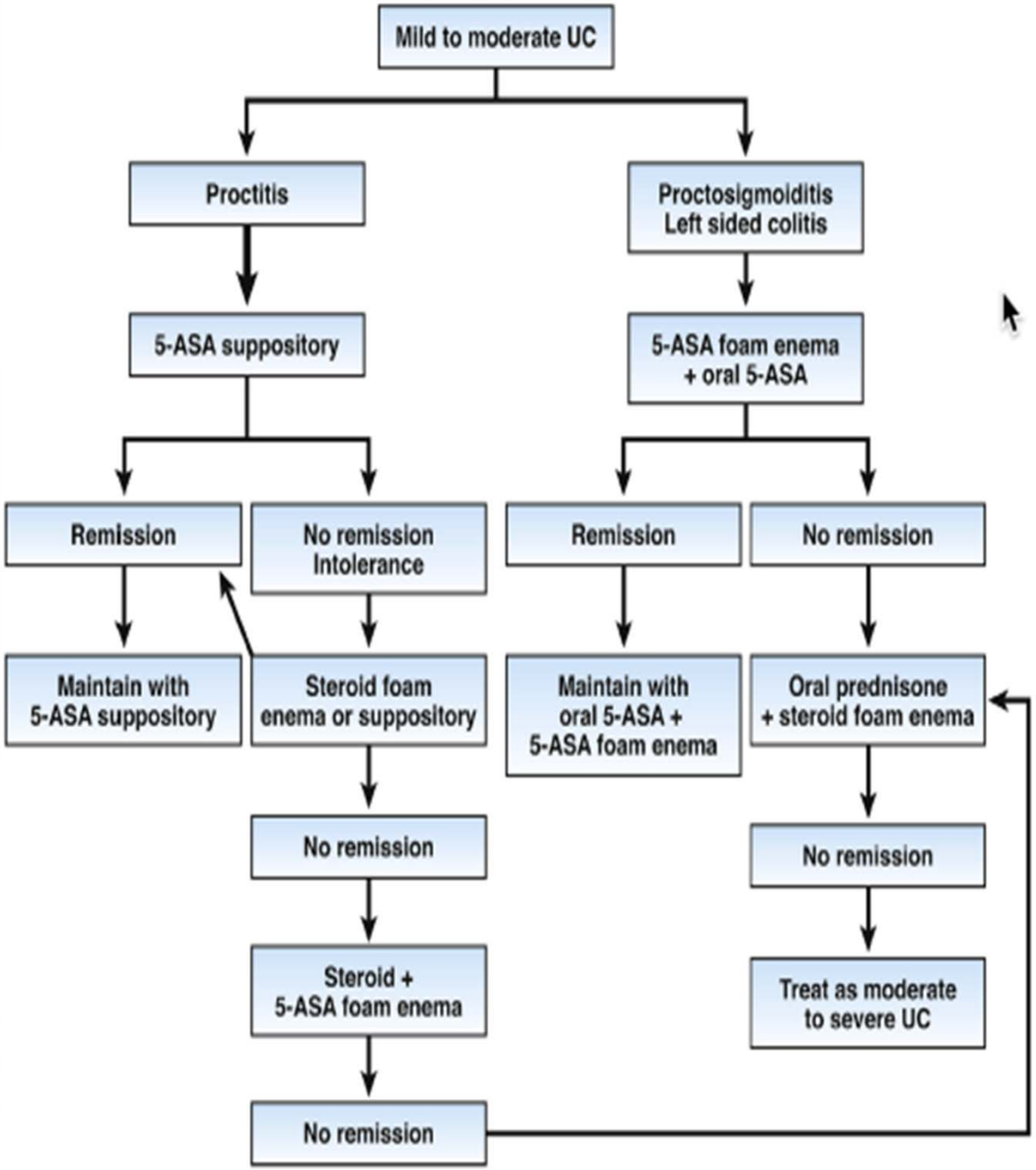


Figure 1. Algorithm for the initial management of ulcerative proctitis, proctosigmoiditis, or left-sided colitis.

Question

- A 27 yr. male with mild limited left sided UC, diagnosed in 2012 is seen in the office for follow up. He has previously used 5ASA with good effect but now has worsening symptoms for 8 wks.
- A) would you add rectal 5ASA
- B) would you give oral steroids
- C) would you give rectal steroids
- D) would you do a colonoscopy
- E) would you do something else

Gastroenterology 2015;148:1035–1058

CONSENSUS STATEMENT

Clinical Practice Guidelines for the Medical Management of Nonhospitalized Ulcerative Colitis: The Toronto Consensus

Brian Bressler,[1,*] **John K. Marshall**,[2,*] Charles N. Bernstein,[3] Alain Bitton,[4] Jennifer Jones,[5] Grigorios I. Leontiadis,[2] Remo Panaccione,[6] A. Hillary Steinhart,[7] Francis Tse,[2] and Brian Feagan,[8] on behalf of the Toronto Ulcerative Colitis Consensus Group

BACKGROUND & AIMS: The medical management of ulcerative colitis (UC) has improved through the development of new therapies and novel approaches that optimize existing drugs. Previous Canadian consensus guidelines addressed the management of severe UC in the hospitalized patient. We now present consensus guidelines for the treatment of ambulatory patients with mild to severe active UC. **METHODS:** A systematic literature search identified studies on the management of UC. The quality of evidence and strength of recommendations were rated according to the Grading of Recommendation Assessment, Development and Evaluation (GRADE) approach. Statements were developed through an iterative online platform and then finalized and voted on by a working group of specialists. **RESULTS:** The participants concluded that the goal of therapy is complete remission, defined as both symptomatic and endoscopic remission without corticosteroid therapy. The consensus includes 34 statements focused on 5 main drug classes: 5-aminosalicylate (5-ASA), corticosteroids, immunosuppressants, anti–tumor necrosis factor (TNF) therapies, and other therapies. Oral and rectal 5-ASA are recommended first-line therapy for mild to moderate UC, with corticosteroid therapy for those who fail to achieve remission. Patients with moderate to severe UC should undergo a course of oral corticosteroid therapy, with transition to 5-ASA, thiopurine, anti-TNF (with or without thiopurine or methotrexate), or vedolizumab maintenance therapy in those who successfully achieve symptomatic remission. For patients with corticosteroid-resistant/dependent UC, anti-TNF or vedolizumab therapy is recommended. Timely assessments of response and remission are critical to ensuring optimal outcomes. **CONCLUSIONS:** Optimal management of UC requires careful patient assessment, evidence-based use of existing therapies, and thorough assessment to define treatment success.

Table 4. Summary of Consensus Recommendations for the Medical Management of UC

Statements regarding 5-ASA

1. 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.*
2. 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.*
3. 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.*
4. 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.*
5. 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.*
6. 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.*
7. 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.*
8. In selected 5-ASA–naive 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.*
9. 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.*
10. 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.*

Statements regarding corticosteroids

11. 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.*
12. 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.*
13. 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.*
14. 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.*
15. 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.*
16. 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.*

Statements regarding immunosuppressants

17. In patients with UC, we recommend against the use of thiopurine monotherapy to induce complete remission. *GRADE: Strong recommendation, low-quality evidence.*
18. 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.*
19. 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.*

Statements regarding anti-TNF therapy

20. 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.*
21. 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.*
22. 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.*
23. 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.*
24. 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.*
25. 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.*
26. 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.*

Table 4. Continued

27. We recommend that dose optimization for patients with UC be informed by therapeutic drug monitoring. *GRADE: Strong recommendation, low-quality evidence.*

Statements regarding other agents

28. 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.*
29. 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.*
30. 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.*
31. 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.*
32. 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.*
33. 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.*
34. 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.*

Topical Therapy in Ulcerative Colitis: Always a Bridesmaid but Never a Bride?

Gastroenterology 2015;149:302–317

REVIEWS IN BASIC AND CLINICAL GASTROENTEROLOGY AND HEPATOLOGY

Robert F. Schwabe and John W. Wiley, Section Editors

Epidemiology, Diagnosis, and Management of Esophageal Adenocarcinoma

Joel H. Rubenstein[1,2] and Nicholas J. Shaheen[3]

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Esophageal adenocarcinoma (EAC) is rapidly increasing in incidence in Western cultures. Barrett's esophagus is the presumed precursor lesion for this cancer. Several other risk factors for this cancer have been described, including chronic heartburn, tobacco use, white race, and obesity. Despite these known associations, most patients with EAC present with symptoms of dysphagia from late-stage tumors; only a small number of patients are identified by screening and surveillance programs. Diagnostic analysis of EAC usually commences with upper endoscopy followed by cross-sectional imaging. Endoscopic ultrasonography is useful to assess the local extent of disease as well as the involvement of regional lymph nodes. T1a EAC may be treated endoscopically, and some patients with T1b disease may also benefit from endoscopic therapy. Locally advanced disease is generally managed with esophagectomy, often accompanied by neoadjuvant chemoradiotherapy or chemotherapy. The prognosis is based on tumor stage; patients with T1a tumors have an excellent prognosis, whereas few patients with advanced disease have long-term survival.

Gastroenterology 2015;149:350–355

Loss of Infliximab Into Feces Is Associated With Lack of Response to Therapy in Patients With Severe Ulcerative Colitis

Johannan F. Brandse,[1,2] Gijs R. van den Brink,[1,2] Manon E. Wildenberg,[2] Desiree van der Kleij,[3] Theo Rispens,[4] Jeroen M. Jansen,[5] Ron A. Mathôt,[6] Cyriel Y. Ponsioen,[1] Mark Löwenberg,[1] and Geert R. A. M. D'Haens[1]

[1]Department of Gastroenterology and Hepatology, Academic Medical Center, Amsterdam, The Netherlands; [2]Tytgat Institute for Liver and Intestinal Research, Amsterdam, The Netherlands; [3]Biologicals Laboratory, Sanquin Laboratory, Amsterdam, The Netherlands; [4]Sanquin Research, Sanquin Laboratory, Amsterdam, The Netherlands; [5]Department of Gastroenterology, Onze Lieve Vrouwe Gasthuis, Amsterdam, The Netherlands; and [6]Department of Hospital Pharmacy, Academic Medical Center, Amsterdam, The Netherlands

BACKGROUND & AIMS: It is not clear why some patients with ulcerative colitis (UC) do not respond to treatment with anti-tumor necrosis factor (TNF) agents, such as infliximab. It could be that some patients have high level of inflammation, with large quantities of TNF to be neutralized by the drug. We investigated whether loss of anti-TNF agents through ulcerated intestinal mucosa reduces the efficacy of these drugs in patients with severe UC. **METHODS:** We collected fecal samples from 30 consecutive patients with moderate to severely active UC during the first 2 weeks of infliximab therapy at the University of Amsterdam hospital. Infliximab concentrations were measured in serum and supernatants of fecal samples using an enzyme-linked immunosorbent assay (Sanquin Biologicals Laboratory, Amsterdam, The Netherlands). Clinical and endoscopic responses were assessed 2 and 8 weeks and 3 months after treatment began. **RESULTS:** Infliximab was detected in 129 of 195 fecal samples (66%); the highest concentrations were measured in the first days after the first infusion. Patients that were clinical nonresponders at week 2 had significantly higher fecal concentrations of infliximab after the first day of treatment than patients with clinical responses (median concentration, 5.01 μg/mL in nonresponders vs 0.54 μg/mL in responders; $P = .0047$). We did not observe a correlation between fecal and serum concentrations of infliximab. **CONCLUSIONS:** Infliximab is lost into stools of patients with UC. High fecal concentrations of infliximab in the first days after therapy begins are associated with primary nonresponse. Additional studies are needed to determine how therapeutic antibodies are lost through the intestinal mucosa and how this process affects treatment response. Clinical trial ID: NL41310.018.12.

Question

- A 26 yr F with a history of CD of TI is seen in the office for follow up. She has been on immuran and infliximab for 2.5 years without flares. She says she wants to stop her meds.
- A) would you stop her immuran
- B) would you stop her biologic
- C) would you image +/- scope
- D) would you tell her to continue meds
- E) would you do something else

Gastroenterology 2015;149:1716–1730

Systematic Review of Effects of Withdrawal of Immunomodulators or Biologic Agents From Patients With Inflammatory Bowel Disease

Joana Torres,[1,*] **Ray K. Boyapati**,[2,*] Nicholas A. Kennedy,[2] Edouard Louis,[3] Jean-Frédéric Colombel,[1] and Jack Satsangi[2]

Little is known about the optimal duration of therapy with an anti-tumor necrosis factor (TNF) agent and/or an immunomodulator for patients with inflammatory bowel disease (IBD). We performed a systematic search of the literature to identify studies reporting after de-escalation (drug cessation or dose reduction) of anti-TNF agents and/or immunomodulators in patients in remission from IBD. Studies were reviewed according to the type of IBD and drug. Rates of relapse, factors associated with relapse, and response to re-treatment were determined. Our search yielded 6315 unique citations; we analyzed findings from 69 studies (18 on de-escalation [drug cessation or dose reduction] of immunomodulator monotherapy, 8 on immunomodulator de-escalation from combination therapy, and 43 on de-escalation of anti-TNF agents, including 3 during pregnancy) comprising 4672 patients. Stopping immunomodulator monotherapy after a period of remission was associated with high rates of relapse in patients with Crohn's disease or ulcerative colitis (approximately 75% of patients experienced a relapse within 5 years after therapy was stopped). Most studies of patients with Crohn's disease who discontinued an immunomodulator after combination therapy found that rates of relapse did not differ from those of patients who continued taking the drug (55%–60% had disease relapse 24 months after they stopped taking the immunomodulator). The only study in patients with ulcerative colitis supported continued immunomodulator use. Approximately 50% of patients who discontinued anti-TNF agents after combination therapy maintained remission 24 months later, but the proportion in remission decreased with time. Markers of disease activity, poor prognostic factors, and complicated or relapsing disease course were associated with future relapse. In conclusion, based on a systematic review, 50% or more of patients with IBD who cease therapy have a disease relapse. Further studies are required to accurately identify subgroups of patients who are good candidates for discontinuation of treatment. The decision to withdraw a drug should be made for each individual based on patient preference, disease markers, consequences of relapse, safety, and cost.

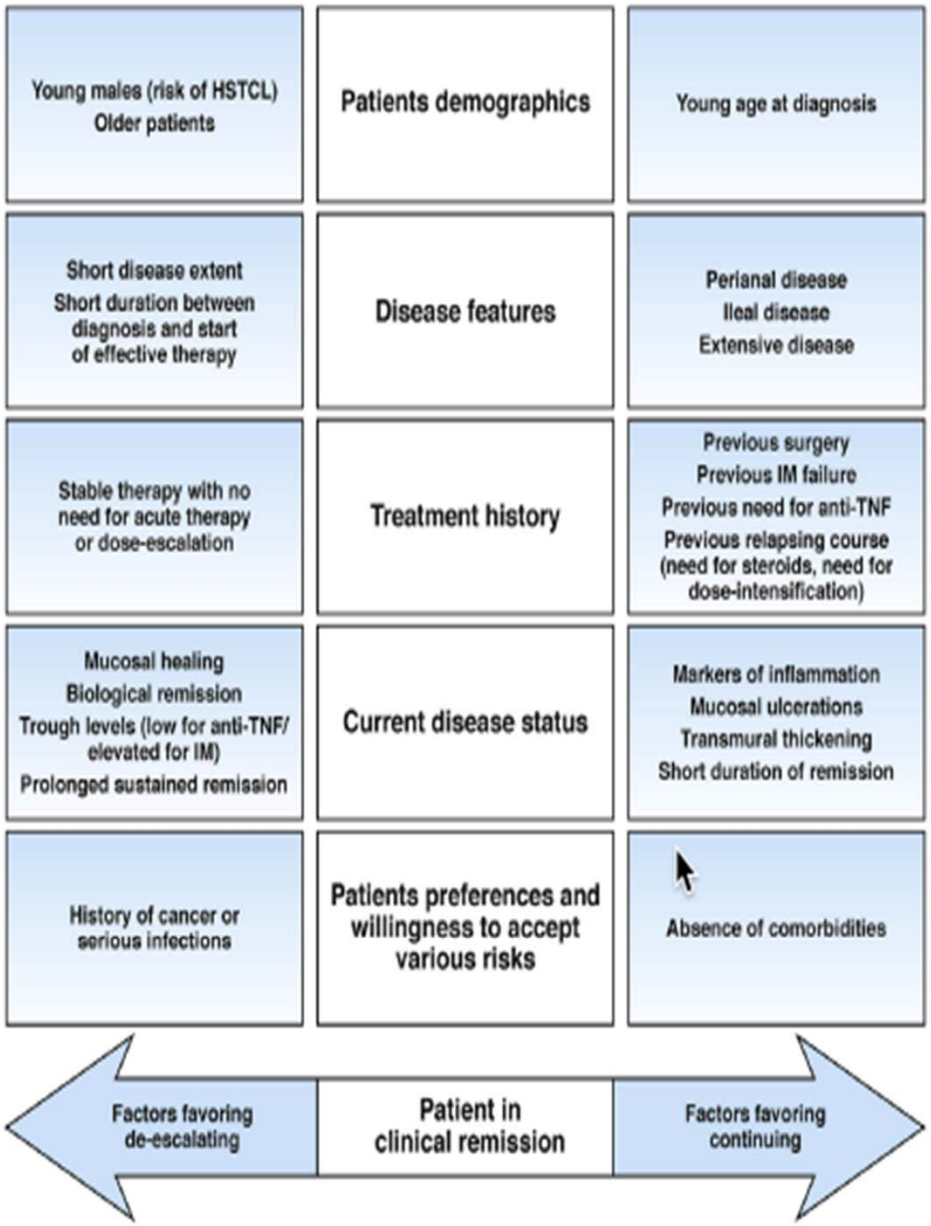

Figure 2. Factors involved in the decision to de-escalate drug therapy in patients with IBD, includes those involving patient demographics, disease features, treatment history, current disease status, and patient preference. HSTCL, hepatosplenic T-cell lymphoma.

Question

- A 75 yr M is seen in the ER with LLQ pain and a mild fever. The ERP has done a CT which suggests diverticulitis. Would you:
- A) give antibiotics
- B) book for a colonoscopy in a week
- C) tell pt to avoid nuts and seeds
- D) all of the above
- E) none of the above

Gastroenterology 2015;149:1944–1949

AGA SECTION

American Gastroenterological Association Institute Guideline on the Management of Acute Diverticulitis

Neil Stollman,[1] Walter Smalley,[2,3] Ikuo Hirano,[4] and AGA Institute Clinical Guidelines Committee

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Table 3. AGA Recommendations on the Management of Acute Diverticulitis

Recommendation	Strength of recommendation	Quality of evidence
The AGA suggests that antibiotics should be used selectively, rather than routinely, in patients with acute uncomplicated diverticulitis.	Conditional	Low
The AGA suggests that colonoscopy be performed after resolution of acute diverticulitis in appropriate candidates to exclude the misdiagnosis of a colonic neoplasm if a high-quality examination of the colon has not been recently performed.	Conditional	Low
The AGA suggests against elective colonic resection in patients with an initial episode of acute uncomplicated diverticulitis. The decision to perform elective prophylactic colonic resection in this setting should be individualized.	Conditional	Very low
The AGA suggests a fiber-rich diet or fiber supplementation in patients with a history of acute diverticulitis.	Conditional	Very low
The AGA suggests against routinely advising patients with a history of diverticulitis to avoid consumption of seeds, nuts, and popcorn.	Conditional	Very low
The AGA suggests against routinely advising patients with a history of diverticulitis to avoid the use of aspirin.	Conditional	Low
The AGA suggests advising patients with a history of diverticulitis to avoid the use of nonaspirin NSAIDs if possible.	Conditional	Very low
The AGA recommends against the use of mesalamine after acute uncomplicated diverticulitis.	Strong	Moderate
The AGA suggests against the use of rifaximin after acute uncomplicated diverticulitis.	Conditional	Very low
The AGA suggests against the use of probiotics after acute uncomplicated diverticulitis.	Conditional	Very low
The AGA suggests advising patients with diverticular disease to consider vigorous physical activity.	Conditional	Very low

Gastroenterology 2015;148:334–343

Mucosal Impedance Discriminates GERD From Non-GERD Conditions

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BACKGROUND & AIMS: Current diagnostic tests for gastroesophageal reflux disease (GERD) are suboptimal and do not accurately and reliably measure chronicity of reflux. A minimally invasive device has been developed to assess esophageal mucosal impedance (MI) as a marker of chronic reflux. We performed a prospective longitudinal study to investigate MI patterns in patients with GERD and common nonreflux conditions, to assess MI patterns before and after treatment with proton pump inhibitors and to compare the performance of MI and wireless pH tests. **METHODS:** We evaluated MI in 61 patients with erosive esophagitis, 81 with nonerosive but pH-abnormal GERD, 93 without GERD, 18 with achalasia, and 15 with eosinophilic esophagitis. MI was measured at the site of esophagitis and at 2, 5, and 10 cm above the squamocolumnar junction in all participants. MI was measured before and after acid suppressive therapy, and findings were compared with those from wireless pH monitoring. **RESULTS:** MI values were significantly lower in patients with GERD (erosive esophagitis or nonerosive but pH-abnormal GERD) or eosinophilic esophagitis than in patients without GERD or patients with achalasia ($P < .001$). The pattern of MI in patients with GERD differed from that in patients without GERD or patients with eosinophilic esophagitis; patients with GERD had low MI closer to the squamocolumnar junction, and values increased axially along the esophagus. These patterns normalized with acid suppressive therapy. MI patterns identified patients with esophagitis with higher levels of specificity (95%) and positive predictive values (96%) than wireless pH monitoring (64% and 40%, respectively). **CONCLUSIONS:** Based on a prospective study using a prototype device, measurements of MI detect GERD with higher levels of specificity and positive predictive values than wireless pH monitoring. Clinical Trials.gov, Number: NCT01556919.

Gastroenterology 2015;148:344–354

Comparative Effectiveness of Immunosuppressants and Biologics for Inducing and Maintaining Remission in Crohn's Disease: A Network Meta-analysis

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BACKGROUND & AIMS: There is controversy regarding the best treatment for patients with Crohn's disease because of the lack of direct comparative trials. We compared therapies for induction and maintenance of remission in patients with Crohn's disease, based on direct and indirect evidence. **METHODS:** We performed systematic reviews of MEDLINE, EMBASE, and Cochrane Central databases, through June 2014. We identified randomized controlled trials (N = 39) comparing methotrexate, azathioprine/6-mercaptopurine, infliximab, adalimumab, certolizumab, vedolizumab, or combined therapies with placebo or an active agent for induction and maintenance of remission in adult patients with Crohn's disease. Pairwise treatment effects were estimated through a Bayesian random-effects network meta-analysis and reported as odds ratios (OR) with a 95% credible interval (CrI). **RESULTS:** Infliximab, the combination of infliximab and azathioprine (infliximab + azathioprine), adalimumab, and vedolizumab were superior to placebo for induction of remission. In pairwise comparisons of anti–tumor necrosis factor agents, infliximab + azathioprine (OR, 3.1; 95% CrI, 1.4–7.7) and adalimumab (OR, 2.1; 95% CrI, 1.0–4.6) were superior to certolizumab for induction of remission. All treatments were superior to placebo for maintaining remission, except for the combination of infliximab and methotrexate. Adalimumab, infliximab, and infliximab + azathioprine were superior to azathioprine/6-mercaptopurine: adalimumab (OR, 2.9; 95% CrI, 1.6–5.1), infliximab (OR, 1.6; 95% CrI, 1.0–2.5), infliximab + azathioprine (OR, 3.0; 95% CrI, 1.7–5.5) for maintenance of remission. Adalimumab and infliximab + azathioprine were superior to certolizumab: adalimumab (OR, 2.5; 95% CrI, 1.4–4.6) and infliximab + azathioprine (OR, 2.6; 95% CrI, 1.3–6.0). Adalimumab was superior to vedolizumab (OR, 2.4; 95% CrI, 1.2–4.6). **CONCLUSIONS:** Based on a network meta-analysis, adalimumab and infliximab + azathioprine are the most effective therapies for induction and maintenance of remission of Crohn's disease.

Gastroenterology 2015;148:324–333

CLINICAL—ALIMENTARY TRACT

Efficacy of Transoral Fundoplication vs Omeprazole for Treatment of Regurgitation in a Randomized Controlled Trial

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BACKGROUND & AIMS: Transoral esophagogastric fundoplication (TF) can decrease or eliminate features of gastroesophageal reflux disease (GERD) in some patients whose symptoms persist despite proton pump inhibitor (PPI) therapy. We performed a prospective, sham-controlled trial to determine if TF reduced troublesome regurgitation to a greater extent than PPIs in patients with GERD. **METHODS:** We screened 696 patients with troublesome regurgitation despite daily PPI use with 3 validated GERD-specific symptom scales, on and off PPIs. Those with at least troublesome regurgitation (based on the Montreal definition) on PPIs underwent barium swallow, esophagogastroduodenoscopy, 48-hour esophageal pH monitoring (off PPIs), and high-resolution esophageal manometry analyses. Patients with GERD and hiatal hernias $\leq$2 cm were randomly assigned to groups that underwent TF and then received 6 months of placebo (n = 87), or sham surgery and 6 months of once- or twice-daily omeprazole (controls, n = 42). Patients were blinded to therapy during follow-up period and reassessed at 2, 12, and 26 weeks. At 6 months, patients underwent 48-hour esophageal pH monitoring and esophagogastroduodenoscopy. **RESULTS:** By intention-to-treat analysis, TF eliminated troublesome regurgitation in a larger proportion of patients (67%) than PPIs (45%) ($P = .023$). A larger proportion of controls had no response at 3 months (36%) than subjects that received TF (11%; $P = .004$). Control of esophageal pH improved after TF (mean 9.3% before and 6.3% after; $P < .001$), but not after sham surgery (mean 8.6% before and 8.9% after). Subjects from both groups who completed the protocol had similar reductions in GERD symptom scores. Severe complications were rare (3 subjects receiving TF and 1 receiving the sham surgery). **CONCLUSIONS:** TF was an effective treatment for patients with GERD symptoms, particularly in those with persistent regurgitation despite PPI therapy, based on evaluation 6 months after the procedure. Clinicaltrials.gov no: NCT01136980.

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CLINICAL—ALIMENTARY TRACT

Development of the Lémann Index to Assess Digestive Tract Damage in Patients With Crohn's Disease

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overall. **CONCLUSIONS:** In a cross-sectional study, we assessed the ability of the Lémann Index to measure cumulative structural bowel damage in patients with CD. Provided further successful validation and good sensitivity to change, the index should be used to evaluate progression of CD and efficacy of treatment.

Question

- You are giving a healthy 55 yr F patient colonoscopy instructions. The patient was found to have polyps 5 years ago. They state the had a 4 L prep in the past and do not want that again. Do you:
- A) give a 2L prep
- B) another type of prep
- C) give prep split over 2 days (day before and day of scope)
- D) do you tell them to take Gatorade
- E) A & C & D
- F) B & C & D

Gastroenterology 2015;149:79–88

Split-Dose Preparations Are Superior to Day-Before Bowel Cleansing Regimens: A Meta-analysis

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BACKGROUND & AIMS: There are different regimens of preparing the colon for colonoscopy, including polyethylene glycol (PEG), sodium phosphate, picosulfate, or oral sulfate solutions. We performed a meta-analysis to determine the efficacy of split-dose vs other colon preparation regimens, the optimal products for use, and the most effective preparation volumes. **METHODS:** We performed systematic searches of MEDLINE, EMBASE, Scopus, CENTRAL, and ISI Web of knowledge databases, from January 1980 to March 2014, for published results from randomized trials that assessed split-dose regimens vs day-before colonoscopy preparation. We excluded studies that included pediatric or hospitalized patients, or patients with inflammatory bowel disease. The primary outcome was efficacy of bowel cleansing. Secondary outcomes included side effects or complications, outcomes of procedures, patients' willingness to repeat the procedure, and the amount of time required for patients to resume daily activities. **RESULTS:** We identified 47 trials that fulfilled our inclusion criteria (n = 13,487 patients). Split-dose preparations provided significantly better colon cleansing than day-before preparations (odds ratio [OR], 2.51; 95% confidence interval, 1.86–3.39), as well as day-before preparations with PEG (OR, 2.60; 95% confidence interval, 1.46–4.63), sodium phosphate (OR, 9.34; 95% confidence interval, 2.12–41.11), or picosulfate (OR, 3.54; 95% confidence interval, 1.95–6.45). PEG split-dose preparations of 3 L or more yielded greater bowel cleanliness than lower-volume split-dose regimens (OR, 1.89; 95% confidence interval, 1.01–3.46), but only in intention-to-treat analysis. A higher proportion of patients were willing to repeat split-dose vs day-before cleansing (OR, 1.90; 95% confidence interval, 1.05–3.46), and low-volume split-dose preparations vs high-volume split-dose preparation (OR, 4.95; 95% confidence interval, 2.21–11.10). There were no differences between preparations in other secondary outcome measures. However, there was variation among studies in definitions and main and secondary outcomes. **CONCLUSIONS:** Based on meta-analysis, split-dose regimens increase the quality of colon cleansing and are preferred by patients compared with day-before preparations. Additional research is required to evaluate oral sulfate solution–based and PEG low-volume regimens further.

Table 3. Outcomes for Split-Dose of any Product vs Day-Before of any Product

Outcome	Number of trials[a] (number of included patients)	OR (95% CI); heterogeneity (*P* value, I^2)	Conclusion
Primary outcome: bowel cleanliness (excellent/good)	32 (8199)	2.51 (1.86–3.39); $P < .01$, 84.8%	Split-dose regimens yield the highest quality of colon cleansing across all types of colonic preparations
Secondary outcome: willingness-to-repeat	14 (4377)	1.90 (1.05–3.46); $P < .01$, 92.8%	Willingness-to-repeat is enhanced by the use of split-dose vs day-before regimens of any product
Secondary outcome: polyp detection rate	2 (159)	0.93 (0.41–2.13); $P < .52$, 0.0%	More trials are required to conclude on procedural outcomes
Secondary outcome: adenoma detection rate	2 (213)	1.52 (0.69–3.32); $P < .19$, 42.2%	
Secondary outcome: side effects and resumption of daily activities	0 to 24 (6434)	See Appendix 2	More uniform definitions across studies are required to conclude on side effects and resumption of daily activities

CI, confidence interval.
[a]Trials with analyzable data.

Conclusions

Split-dose regimens yield the highest quality of colon cleansing across all types of colonic preparations. Willingness-to-repeat is enhanced by the use of split-dose vs day-before regimens of any product, and by the adoption of low- vs high-volume PEG split-dose regimens. More uniform definitions across studies are required to conclude on other secondary outcomes such as side effects, polyp and adenoma detection, and resumption of daily activities. Future research must focus on comparing split-PEG dosing of large and low-volumes, split-dose vs same-day preparations, and direct evaluations of PEG-based vs PICO and OSS preparations.

Question

- A 28 F with left sided, prev. moderate UC is in the office and asks about fecal transplant as a treatment for her UC. She has some concerns about side effects. Do you tell her:
- A) You do not advise FMT because it does not work
- B) Go see Paul Moayyedi
- C) Tell her the procedure is safe
- D) Tell her you would consider FMT if she gets more symptoms

Gastroenterology 2015;149:223–237

AGA SECTION

Update on Fecal Microbiota Transplantation 2015: Indications, Methodologies, Mechanisms, and Outlook

Colleen R. Kelly,[1] Stacy Kahn,[2] Purna Kashyap,[3] Loren Laine,[4,5] David Rubin,[2] Ashish Atreja,[6] Thomas Moore,[7] and Gary Wu[8]

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The community of microorganisms within the human gut (or microbiota) is critical to health and functions with a level of complexity comparable to that of an organ system. Alterations of this ecology (or dysbiosis) have been implicated in a number of disease states, and the prototypical example is *Clostridium difficile* infection (CDI). Fecal microbiota transplantation (FMT) has been demonstrated to durably alter the gut microbiota of the recipient and has shown efficacy in the treatment of patients with recurrent CDI. There is hope that FMT may eventually prove beneficial for the treatment of other diseases associated with alterations in gut microbiota, such as inflammatory bowel disease, irritable bowel syndrome, and metabolic syndrome, to name a few. Although the basic principles that underlie the mechanisms by which FMT shows therapeutic efficacy in CDI are becoming apparent, further research is needed to understand the possible role of FMT in these other conditions. Although relatively simple to perform, questions regarding both short-term and long-term safety as well as the complex and rapidly evolving regulatory landscape has limited widespread use. Future work will focus on establishing best practices and more robust safety data than exist currently, as well as refining FMT beyond current "whole-stool" transplants to increase safety and tolerability. Encapsulated formulations, full-spectrum stool-based products, and defined microbial consortia are all in the immediate future.

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Findings From a Randomized Controlled Trial of Fecal Transplantation for Patients With Ulcerative Colitis

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BACKGROUND & AIMS: Several case series have reported the effects of fecal microbiota transplantation (FMT) for ulcerative colitis (UC). We assessed the efficacy and safety of FMT for patients with UC in a double-blind randomized trial. **METHODS:** Patients with mild to moderately active UC (n = 50) were assigned to groups that underwent FMT with feces from healthy donors or were given autologous fecal microbiota (control); each transplant was administered via nasoduodenal tube at the start of the study and 3 weeks later. The study was performed at the Academic Medical Center in Amsterdam from June 2011 through May 2014. The composite primary end point was clinical remission (simple clinical colitis activity index scores ≤2) combined with ≥1-point decrease in the Mayo endoscopic score at week 12. Secondary end points were safety and microbiota composition by phylogenetic microarray in fecal samples. **RESULTS:** Thirty-seven patients completed the primary end point assessment. In the intention-to-treat analysis, 7 of 23 patients who received fecal transplants from healthy donors (30.4%) and 5 of 25 controls (20.0%) achieved the primary end point ($P = .51$). In the per-protocol analysis, 7 of 17 patients who received fecal transplants from healthy donors (41.2%) and 5 of 20 controls (25.0%) achieved the primary end point ($P = .29$). Serious adverse events occurred in 4 patients (2 in the FMT group), but these were not considered to be related to the FMT. At 12 weeks, the microbiota of responders in the FMT group was similar to that of their healthy donors; remission was associated with proportions of *Clostridium* clusters IV and XIVa. **CONCLUSIONS:** In this phase 2 trial, there was no statistically significant difference in clinical and endoscopic remission between patients with UC who received fecal transplants from healthy donors and those who received their own fecal microbiota, which may be due to limited numbers. However, the microbiota of responders had distinct features from that of nonresponders, warranting further study. ClinicalTrials.gov Number: NCT01650038.

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Fecal Microbiota Transplantation Induces Remission in Patients With Active Ulcerative Colitis in a Randomized Controlled Trial

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BACKGROUND & AIMS: Ulcerative colitis (UC) is difficult to treat, and standard therapy does not always induce remission. Fecal microbiota transplantation (FMT) is an alternative approach that induced remission in small series of patients with active UC. We investigated its safety and efficacy in a placebo-controlled randomized trial. **METHODS:** We performed a parallel study of patients with active UC without infectious diarrhea. Participants were examined by flexible sigmoidoscopy when the study began and then were randomly assigned to groups that received FMT (50 mL, via enema, from healthy anonymous donors; n = 38) or placebo (50 mL water enema; n = 37) once weekly for 6 weeks. Patients, clinicians, and investigators were blinded to the groups. The primary outcome was remission of UC, defined as a Mayo score ≤2 with an endoscopic Mayo score of 0, at week 7. Patients provided stool samples when the study began and during each week of FMT for microbiome analysis. The trial was stopped early for futility by the Data Monitoring and Safety Committee, but all patients already enrolled in the trial were allowed to complete the study. **RESULTS:** Seventy patients completed the trial (3 dropped out from the placebo group and 2 from the FMT group). Nine patients who received FMT (24%) and 2 who received placebo (5%) were in remission at 7 weeks (a statistically significant difference in risk of 17%; 95% confidence interval, 2%–33%). There was no significant difference in adverse events between groups. Seven of the 9 patients in remission after FMT received fecal material from a single donor. Three of the 4 patients with UC ≤1 year entered remission, compared with 6 of 34 of those with UC >1 year ($P = .04$, Fisher's exact test). Stool from patients receiving FMT had greater microbial diversity, compared with baseline, than that of patients given the placebo ($P = .02$, Mann-Whitney U test). **CONCLUSIONS:** FMT induces remission in a significantly greater percentage of patients with active UC than placebo, with no difference in adverse events. Fecal donor and time of UC appear to affect outcomes. ClinicalTrials.gov Number: NCT01545908.

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Trough Concentrations of Infliximab Guide Dosing for Patients With Inflammatory Bowel Disease

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BACKGROUND & AIMS: Infliximab, a tumor necrosis factor antagonist, is effective for treating patients with Crohn's disease (CD) and ulcerative colitis (UC). We aimed to determine whether dosing based on therapeutic drug monitoring increases rate of remission and whether continued concentration-based dosing is superior to clinically based dosing of infliximab for maintaining remission in patients with CD and UC. **METHODS:** We performed a 1-year randomized controlled trial at a tertiary referral center, including 263 adults (178 with CD and 85 with UC) with stable responses to maintenance infliximab therapy. Doses were escalated or reduced using an algorithm to reach a target trough concentration (TC) of 3–7 μg/mL in all patients (optimization phase). Patients were randomly assigned (1:1) to groups that received infliximab dosing based on their clinical features (n = 123) or continued dosing based on TCs (n = 128) (maintenance phase). The primary end point was clinical and biochemical remission at 1 year after the optimization phase. **RESULTS:** At screening, 115 of 263 patients had a TC of infliximab of 3–7 μg/mL (43.7%). Of 76 patients with TCs <3 μg/mL, 69 patients (91%) achieved TCs of 3–7 μg/mL after dose escalation. This resulted in a higher proportion of CD patients in remission than before dose escalation (88% vs 65%; $P = .020$) and a decrease in the median concentration of C-reactive protein, compared with before the dose increase (3.2 vs 4.3 mg/L; $P < .001$); these changes were not observed in patients with UC. Of 72 patients with TCs >7 μg/mL, 67 patients (93%) achieved TCs of 3–7 μg/mL after dose reduction. This resulted in a 28% reduction in drug cost from before dose reduction ($P < .001$). Sixty-six percent of patients whose dosing was based on clinical features and 69% whose dosing was based on TC achieved remission, the primary end point ($P = .686$). Disease relapsed in 21 patients who received clinically based dosing (17%) and 9 patients who received concentration-based dosing (7%) ($P = .018$). **CONCLUSIONS:** Targeting patients' infliximab TCs to 3–7 μg/mL results in a more efficient use of the drug. After dose optimization, continued concentration-based dosing was not superior to clinically based dosing for achieving remission after 1 year, but was associated with fewer flares during the course of treatment. ClinicalTrialsRegister.eu number: 2011-002061-38.

COVERING THE COVER

Anson W. Lowe and Richard H. Moseley, Section Editors

Infliximab Dosing for Patients With Inflammatory Bowel Disease, Based on Trough Levels

EDITORIALS

Drug Level–based Anti-Tumor Necrosis Factor Therapy: Ready for Prime Time?

Gastroenterology 2015;148:517–532

REVIEWS IN BASIC AND CLINICAL GASTROENTEROLOGY AND HEPATOLOGY

Robert F. Schwabe and John W. Wiley, Section Editors

Herbal Products and the Liver: A Review of Adverse Effects and Mechanisms

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Gastroenterology 2015;148:639–651

CONSENSUS STATEMENT

SCENIC International Consensus Statement on Surveillance and Management of Dysplasia in Inflammatory Bowel Disease

Loren Laine,[1,2] Tonya Kaltenbach,[3] Alan Barkun,[4] Kenneth R. McQuaid,[5] Venkataraman Subramanian,[6] and Roy Soetikno,[3] for the SCENIC Guideline Development Panel

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Table 2. Summary of Recommendations for Surveillance and Management of Dysplasia in Patients With Inflammatory Bowel Disease

Detection of dysplasia on surveillance colonoscopy

1. When performing surveillance with white-light colonoscopy, high definition is recommended rather than standard definition (strong recommendation, low-quality evidence).
2. When performing surveillance with standard-definition colonoscopy, chromoendoscopy is recommended rather than white-light colonoscopy (strong recommendation, moderate-quality evidence).
3. When performing surveillance with high-definition colonoscopy, chromoendoscopy is suggested rather than white-light colonoscopy (conditional recommendation, low-quality evidence).
4. When performing surveillance with standard-definition colonoscopy, narrow-band imaging is not suggested in place of white-light colonoscopy (conditional recommendation, low-quality evidence).
5. When performing surveillance with high-definition colonoscopy, narrow-band imaging is not suggested in place of white-light colonoscopy (conditional recommendation, moderate-quality evidence).
6. When performing surveillance with image-enhanced high-definition colonoscopy, narrow-band imaging is not suggested in place of chromoendoscopy (conditional recommendation, moderate-quality evidence).

Management of dysplasia discovered on surveillance colonoscopy

7. After complete removal of endoscopically resectable polypoid dysplastic lesions, surveillance colonoscopy is recommended rather than colectomy (strong recommendation, very low-quality evidence).
8. After complete removal of endoscopically resectable nonpolypoid dysplastic lesions, surveillance colonoscopy is suggested rather than colectomy (conditional recommendation, very low-quality evidence).
9. For patients with endoscopically invisible dysplasia (confirmed by a GI pathologist) referral is suggested to an endoscopist with expertise in IBD surveillance using chromoendoscopy with high-definition colonoscopy (conditional recommendation, very low-quality evidence).

Table 5. Suggested Steps for Implementation of Chromoendoscopy Into Endoscopic Practice

Equipment	
Colonoscope	High-definition colonoscope, monitor, and cables
Accessories	Apply dye via: Water jet channel by using water pump attached to the endoscope activated via foot pedal or Spray catheter: length 240 cm, endoscope accessory channel 2.8 mm
Contrast agent	Indigo carmine, 5-mL ampule (0.8%) Methylene blue, 10-mL ampule (1%)
Procedure and protocol	
Time allotment	Consider doubling colonoscopy time slot initially during the learning curve period.
Standard operating procedure	Complete colonoscopy to cecum. Lavage with water and suction during intubation. Prepare dye solution during insertion for application via the foot pump or spray. Indigo carmine (0.03%): mix 2 5-mL ampules of 0.8% indigo carmine with 250 mL water. Methylene blue (0.04%): mix one 10-mL ampule of 1% methylene blue with 240 mL water. If using a foot pump: once the cecum is intubated, the water irrigation can be exchanged with the contrast solution. Apply the dye solution in a circumferential technique while withdrawing the colonoscope. Direct spray to the anti-gravity side. If using a spray catheter: the dye spray catheter is inserted into the biopsy channel; the catheter tip should protrude 2-3 cm from the endoscope. Apply dye solution segmentally by using a rotational technique while withdrawing the colonoscope to cover the surface mucosa with dye. Suction any excess solution after approximately 1 minute to aid mucosal visualization. Focus on 20-30–cm segments sequentially with reinsertion of the endoscope to the proximal extent of each segment before slow withdrawal and mucosal visualization. Targeted dye spray for suspicious lesions: Prepare more concentrated dye solution for application. Indigo carmine (0.13%): mix one 5-mL ampule of 0.8% indigo carmine with 25 mL water. Methylene blue (0.2%): mix one 10-mL ampule of 1% methylene blue with 40 mL water. Spray about 30 mL directly from a 60-mL syringe through the biopsy channel. Remove endoscopically resectable suspicious lesions by using polypectomy or endoscopic mucosal resection. Do targeted biopsies of any unresectable abnormality visualized through chromoendoscopy to diagnose dysplasia. Do biopsies of flat area surrounding lesions to assess for dysplasia. Consider tattoo of suspicious dysplastic lesions arising from flat mucosa or not amenable to complete removal. Recommendations regarding the need to perform random, non-targeted biopsies for detection of dysplasia vary. If biopsies for dysplasia are not done, 2 random biopsies in every bowel segment are commonly recommended to document microscopic disease activity.

Serial Fecal Calprotectin Measurements to Detect Endoscopic Recurrence in Postoperative Crohn's Disease: Is Colonoscopic Surveillance No Longer Needed?

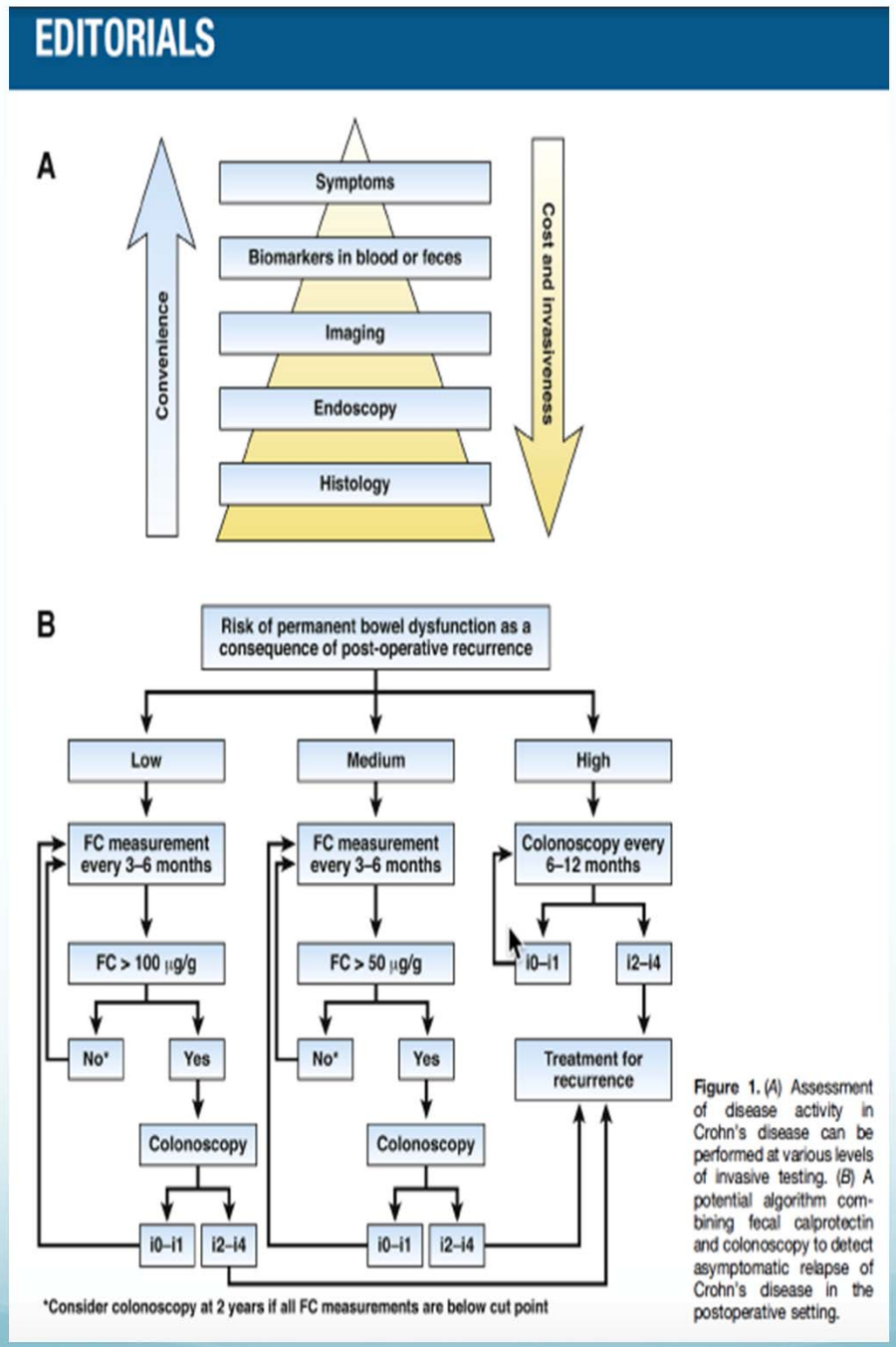


Figure 1. (*A*) Assessment of disease activity in Crohn's disease can be performed at various levels of invasive testing. (*B*) A potential algorithm combining fecal calprotectin and colonoscopy to detect asymptomatic relapse of Crohn's disease in the postoperative setting.

Gastroenterology 2015;148:948–957

Accuracy of Capsule Colonoscopy in Detecting Colorectal Polyps in a Screening Population

Douglas K. Rex,[1] Samuel N. Adler,[2] James Aisenberg,[3] Wilmot C. Burch Jr,[4] Cristina Carretero,[5] Yehuda Chowers,[6] Steven A. Fein,[7] Steven E. Fern,[8] Ignacio Fernandez-Urien Sainz,[9] Alexander Fich,[10] Eyal Gal,[11] John C. Horlander Sr,[12] Kim L. Isaacs,[13] Revital Kariv,[14] Adi Lahat,[15] Wai-Keung Leung,[16] Pramod R. Malik,[17] Doug Morgan,[18] Neofytos Papageorgiou,[19] David P. Romeo,[20] Smita S. Shah,[21] and Matti Waterman[6]

CONCLUSIONS: In an average-risk screening population, technically adequate capsule colonoscopy identified individuals with 1 or more conventional adenomas 6 mm or larger with 88% sensitivity and 82% specificity. Capsule performance seems adequate for patients who cannot undergo colonoscopy or who had incomplete colonoscopies. Additional studies are needed to improve capsule detection of serrated lesions. Clinicaltrials.gov number: NCT01372878.

Gastroenterology 2015;148:938–947

Measurement of Fecal Calprotectin Improves Monitoring and Detection of Recurrence of Crohn's Disease After Surgery

Emily K. Wright,[1,2] Michael A. Kamm,[1,2] Peter De Cruz,[1,2] Amy L. Hamilton,[1,2] Kathryn J. Ritchie,[1] Efrosinia O. Krejany,[1] Steven Leach,[3] Alexandra Gorelik,[4] Danny Liew,[4] Lani Prideaux,[1,2] Ian C. Lawrance,[5,6] Jane M. Andrews,[7,8] Peter A. Bampton,[9,10] Simon L. Jakobovits,[11,12] Timothy H. Florin,[13] Peter R. Gibson,[11,12] Henry Debinski,[15] Finlay A. Macrae,[2,16] Douglas Samuel,[17] Ian Kronborg,[18] Graeme Radford-Smith,[14,19] Warwick Selby,[20] Michael J. Johnston,[1] Rodney Woods,[1] P. Ross Elliott,[1] Sally J. Bell,[1] Steven J. Brown,[1] William R. Connell,[1] Andrew S. Day,[21] Paul V. Desmond,[1,2] and Richard B. Gearry[22]

Gastroenterology 2015;148:967–977

Decreasing Mortality Among Patients Hospitalized With Cirrhosis in the United States From 2002 Through 2010

Monica L. Schmidt,[1] A. Sidney Barritt,[2] Eric S. Orman,[3] and Paul H. Hayashi[2]

[1]University of North Carolina Liver Center and Gillings School of Global Public Health, [2]Division of Gastroenterology and Hepatology, University of North Carolina, Chapel Hill, North Carolina; [3]Division of Gastroenterology and Hepatology, Indiana University, Indianapolis, Indiana

BACKGROUND & AIMS: It is not clear whether evidence-based recommendations for inpatient care of patients with cirrhosis are implemented widely or are effective in the community. We investigated changes in inpatient outcomes and associated features over time. **METHODS:** By using the Healthcare Cost and Utilization Project, National Inpatient Sample, we analyzed 781,515 hospitalizations of patients with cirrhosis from 2002 through 2010. We compared data with those from equal numbers of hospitalizations of patients without cirrhosis and patients with congestive heart failure (CHF), matched for age, sex, and year of discharge. The primary outcome was a change in discharge status over time. Factors associated with outcomes were analyzed by Poisson modeling. **RESULTS:** The mortality of patients with and without cirrhosis, and patients with CHF, decreased over time. The absolute decrease was significantly greater for patients with cirrhosis (from 9.1% to 5.4%) than for patients without cirrhosis (from 2.6% to 2.1%) or patients with CHF (from 2.5% to 1.4%) ($P < .01$). However, relative decreases were similar for patients with cirrhosis (41%) and patients with CHF (44%). For patients with cirrhosis, the independent mortality risk ratio decreased steadily to 0.50 by 2010 (95% confidence interval, 0.48–0.52), despite patients' increasing age and comorbidities. Hepatorenal syndrome, hepatocellular carcinoma, variceal bleeding, and spontaneous bacterial peritonitis were associated with a higher mortality rate, but the independent mortality risks for each decreased steadily. Sepsis was associated strongly with increased mortality, and the risk increased over time. **CONCLUSIONS:** Among patients with cirrhosis in the United States, inpatient mortality decreased steadily from 2002 through 2010, despite increases in patient age and medical complexity. Improvements in cirrhosis care may have contributed to increases in patient survival beyond those attributable to general improvements in inpatient care. Further improvements might require an increased use of proven therapies and the development of new treatments—particularly for sepsis.

Question

- A 58 yr F who says her mom had CRC at age 59 is seen in the office. She had a colonoscopy done elsewhere 5 yrs ago and had no polyps. Do you:
- A) book her for colonoscopy
- B) tell her to wait for another colonoscopy
- C) do something else

Family History of Colorectal Cancer: It Is Time to Rethink Screening Recommendations

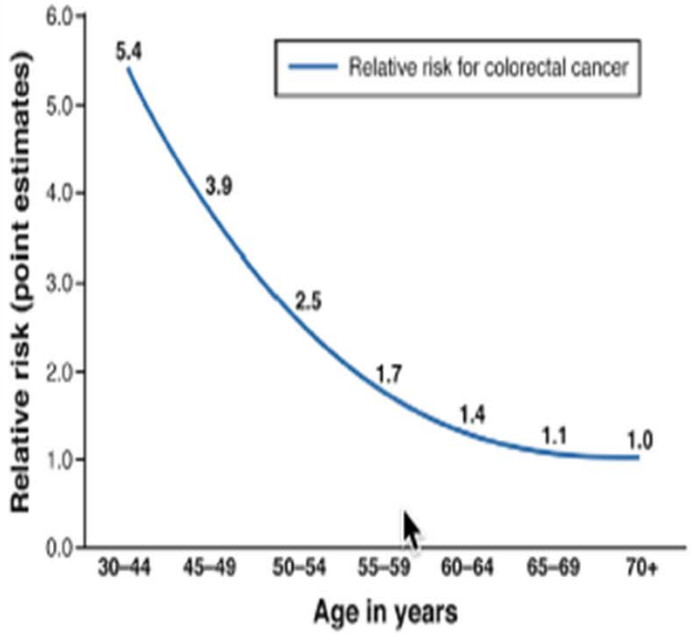


Figure 1. Relative risk for the association between family history of colorectal cancer and disease risk according to age. Note: The data for this figure were extrapolated from data reported by Fuchs et al.[5] The numbers shown are the point estimates reported for each age group.

Gastroenterology 2015;149:1425–1437

Personalizing Colonoscopy Screening for Elderly Individuals Based on Screening History, Cancer Risk, and Comorbidity Status Could Increase Cost Effectiveness

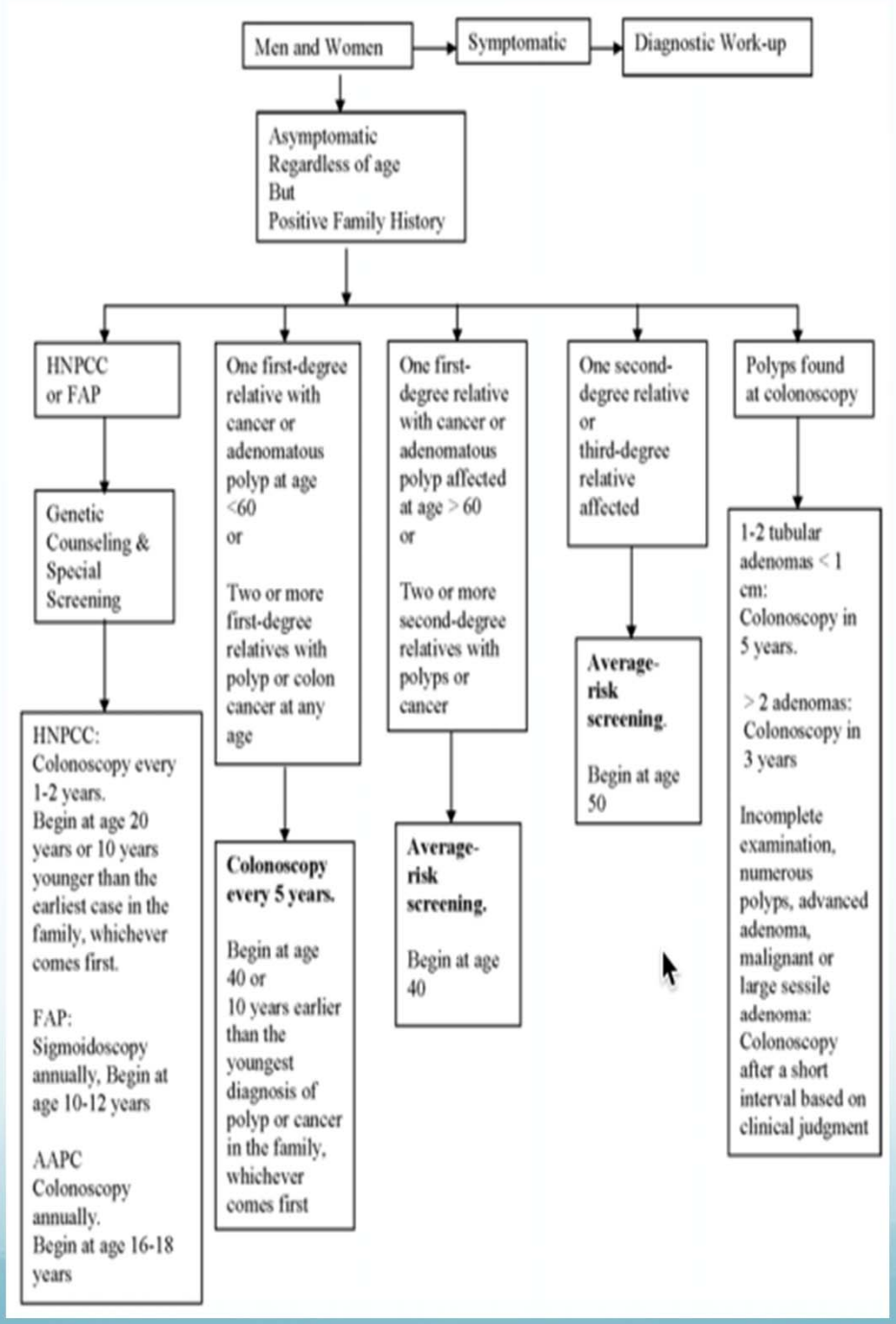
Frank van Hees,[1,*] **Sameer D. Saini**,[2,3,*] Iris Lansdorp-Vogelaar,[1] Sandeep Vijan,[2,3] Reinier G. S. Meester,[1] Harry J. de Koning,[1] Ann G. Zauber,[4] and Marjolein van Ballegooijen[1]

[1]Department of Public Health, Erasmus University Medical Center, Rotterdam, the Netherlands; [2]Veteran Affairs Health Services Research and Development Center for Clinical Management Research; [3]Department of Internal Medicine, University of Michigan Medical School, Ann Arbor, Michigan; and [4]Department of Epidemiology and Biostatistics, Memorial Sloan Kettering Cancer Center, New York, New York

BACKGROUND & AIMS: Colorectal cancer (CRC) screening decisions for elderly individuals are often made primarily on the basis of age, whereas other factors that influence the effectiveness and cost effectiveness of screening are often not considered. We investigated the relative importance of factors that could be used to identify elderly individuals most likely to benefit from CRC screening and determined the maximum ages at which screening remains cost effective based on these factors. **METHODS:** We used a microsimulation model (Microsimulation Screening Analysis-Colon) calibrated to the incidence of CRC in the United States and the prevalence of adenomas reported in autopsy studies to determine the appropriate age at which to stop colonoscopy screening in 19,200 cohorts (of 10 million individuals), defined by sex, race, screening history, background risk for CRC, and comorbidity status. We applied a willingness-to-pay threshold of $100,000 per quality-adjusted life-year (QALY) gained. **RESULTS:** Less intensive screening history, higher background risk for CRC, and fewer comorbidities were associated with cost-effective screening at older ages. Sex and race had only a small effect on the appropriate age to stop screening. For some individuals likely to be screened in current practice (for example, 74-year-old white women with moderate comorbidities, half the average background risk for CRC, and negative findings from a screening colonoscopy 10 years previously), screening resulted in a loss of QALYs, rather than a gain. For some individuals unlikely to be screened in current practice (for example, 81-year-old black men with no comorbidities, an average background risk for CRC, and no previous screening), screening was highly cost effective. Although screening some previously screened, low-risk individuals was not cost effective even when they were 66 years old, screening some healthy, high-risk individuals remained cost effective until they reached the age of 88 years old. **CONCLUSIONS:** The current approach to CRC screening in elderly individuals, in which decisions are often based primarily on age, is inefficient, resulting in underuse of screening for some and overuse of screening for others. CRC screening could be more effective and cost effective if individual factors for each patient are considered.

Canadian Association of Gastroenterology and the Canadian Digestive Health Foundation: Guidelines on colon cancer screening

Desmond Leddin MB FRCPC[1], Richard Hunt MB FRCPC FACG FRCPEd[2], Malcolm Champion MB ChB MRCS LRCP FRCPUK FRCPC[3], Alan Cockeram MD FRCPC DABIM[4], Nigel Flook MD CCFP FCFP[5], Michael Gould MD FRCPC[6], Young-In Kim MD FRCPC[6], Jonathan Love MD FRCPC[4], David Morgan MD FRCPC MSc[2], Susan Natsheh MD FRCPC BMSc[7], Dan Sadowski MD FRCPC ABIM[5], for the Canadian Association of Gastroenterology and the Canadian Digestive Health Foundation committee on colon cancer screening


Men and Women
Symptomatic
Diagnostic Work-up
Asymptomatic
Regardless of age
But
Positive Family History
HNPCC
or FAP
Genetic
Counseling &
Special
Screening
HNPCC:
Colonoscopy every
1-2 years.
Begin at age 20
years or 10 years
younger than the
earliest case in the
family, whichever
comes first.
FAP:
Sigmoidoscopy
annually, Begin at
age 10-12 years
AAPC
Colonoscopy
annually.
Begin at age 16-18
years
One first-degree
relative with
cancer or
adenomatous
polyp at age
<60
or
Two or more
first-degree
relatives with
polyp or colon
cancer at any
age
Colonoscopy
every 5 years.
Begin at age
40 or
10 years earlier
than the
youngest
diagnosis of
polyp or cancer
in the family,
whichever
comes first
One first-
degree relative
with cancer or
adenomatous
polyp affected
at age > 60
or
Two or more
second-degree
relatives with
polyps or
cancer
Average-
risk
screening.
Begin at age
40
One second-
degree relative
or
third-degree
relative
affected
Average-
risk
screening.
Begin at age
50
Polyps found
at colonoscopy
1-2 tubular
adenomas < 1
cm:
Colonoscopy in
5 years.
> 2 adenomas:
Colonoscopy in
3 years
Incomplete
examination,
numerous
polyps, advanced
adenoma,
malignant or
large sessile
adenoma:
Colonoscopy
after a short
interval based on
clinical judgment

COVERING THE COVER

Anson W. Lowe and Richard H. Moseley, Section Editors

Low FODMAPs Versus Traditional Dietary Advice for Treatment of Irritable Bowel Syndrome

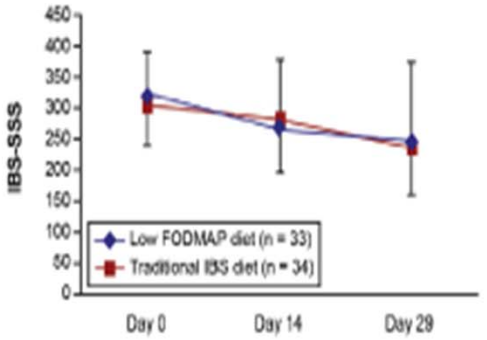


Figure 1. IBS symptom severity (mean ± SD) in patients who completed the intervention. IBS symptom severity measured by IBS-SSS was reduced in both groups at the end of the intervention period (day 29) compared with baseline ($P < .001$ in both groups), whereas at day 14, the reduction in the IBS-SSS reached statistical significance in the low-FODMAP group ($P = .002$), with a trend in the same direction in the traditional IBS diet group ($P = .051$). No differences between the groups were detected.

Gastroenterology 2015;149:1438–1445

Incidence and Mortality of Colorectal Cancer in Individuals With a Family History of Colorectal Cancer

Robert E. Schoen,[1] Anthony Razzak,[1] Kelly J. Yu,[2] Sonja I. Berndt,[3] Kevin Firl,[3] Thomas L. Riley,[4] and Paul F. Pinsky[2]

[1]Division of Gastroenterology, Hepatology and Nutrition, University of Pittsburgh, Pittsburgh, Pennsylvania; [2]Division of Cancer Prevention, National Cancer Institute, Bethesda, Maryland; [3]Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, Maryland; and [4]Information Management Services, Inc., Rockville, Maryland

Table 2. Relationship Between Family History of CRC and Incident CRC

Factor	No. of cases of CRC (n = 2090)	Person-years	Rate (per 10,000 PY)	MV adjusted hazard ratio (95% CI)[a]	*P* value
Family history of CRC[b]					
No	1817	1,423,420	12.8	1.00 (ref)	<.0001
Yes	273	165,057	16.5	1.30 (1.10–1.50)	
No. of affected FDRs					
0 (no FH)	1817	1,423,420	12.8	1.00 (ref)	.008[c]
1 FDR	238	151,995	15.7	1.23 (1.07–1.42)	
≥2 FDR	35	13,062	26.8	2.04 (1.44–2.86)	
Age at diagnosis of affected FDR[d]					
No FH	1817	1,423,420	12.8	1.00 (ref)	.18[e]
FDR diagnosed at >70	88	59,047	14.9	1.15 (0.92–1.44)	
FDR diagnosed 60–70	97	57,008	17.0	1.33 (1.09–1.63)	
FDR diagnosed <60	81	45,368	17.9	1.46 (1.17–1.81)	

FDR, first degree relative; FH, family history; CRC, colorectal cancer; PY, person-years.

[a]Multivariate (MV) adjustment including trial arm, age, sex, prior FOBT, prior lower GI endoscopy, aspirin/NSAID use, and body mass index.

[b]Defined as positive FH in a first degree relative.

[c]*P* value is *P* trend for increasing number of affected FDRs among those with a family history of CRC.

[d]When there are more than 1 affected FDRs, the age at diagnosis is the youngest affected FDR. In 7 subjects, the age at diagnosis of CRC in the FDR was unknown.

[e]*P* value is *P* trend for increasing age at diagnosis of FDR. These estimates include subjects with ≥2 FDRs with CRC.

Question

- A 33yr F, previously diagnosed with IBS is seen in the office. She complains of fluctuating BM but is bothered more by gas and bloating. Do you:
- A) tell her to take more fibre
- B) give her info on the FODMAP diet
- C) Tell her to eat another kind of diet
- D) give her amytriptyline

Gastroenterology 2015;149:1399–1407

Diet Low in FODMAPs Reduces Symptoms of Irritable Bowel Syndrome as Well as Traditional Dietary Advice: A Randomized Controlled Trial

Lena Böhn,[1,2] Stine Störsrud,[1,2] Therese Liljebo,[3] Lena Collin,[4] Perjohan Lindfors,[4,5] Hans Törnblom,[1,2] and Magnus Simrén[1,2]

BACKGROUND & AIMS: A diet with reduced content of fermentable short-chain carbohydrates (fermentable oligo-, di-, monosaccharides, and polyols [FODMAPs]) has been reported to be effective in the treatment of patients with irritable bowel syndrome (IBS). However, there is no evidence of its superiority to traditional dietary advice for these patients. We compared the effects of a diet low in FODMAPs with traditional dietary advice in a randomized controlled trial of patients with IBS. **METHODS:** We performed a multi-center, parallel, single-blind study of 75 patients who met Rome III criteria for IBS and were enrolled at gastroenterology outpatient clinics in Sweden. Subjects were randomly assigned to groups that ate specific diets for 4 weeks—a diet low in FODMAPs (n = 38) or a diet frequently recommended for patients with IBS (ie, a regular meal pattern; avoidance of large meals; and reduced intake of fat, insoluble fibers, caffeine, and gas-producing foods, such as beans, cabbage, and onions), with greater emphasis on how and when to eat rather than on what foods to ingest (n = 37). Symptom severity was assessed using the IBS Symptom Severity Scale, and patients completed a 4-day food diary before and at the end of the intervention. **RESULTS:** A total of 67 patients completed the dietary intervention (33 completed the diet low in FODMAPs, 34 completed the traditional IBS diet). The severity of IBS symptoms was reduced in both groups during the intervention ($P < .0001$ in both groups before vs at the end of the 4-week diet), without a significant difference between the groups ($P = .62$). At the end of the 4-week diet period, 19 patients (50%) in the low-FODMAP group had reductions in IBS severity scores $\geq$50 compared with baseline vs 17 patients (46%) in the traditional IBS diet group ($P = .72$). Food diaries demonstrated good adherence to the dietary advice. **CONCLUSIONS:** A diet low in FODMAPs reduces IBS symptoms as well as traditional IBS dietary advice. Combining elements from these 2 strategies might further reduce symptoms of IBS. ClinicalTrials.gov ID NCT02107625.

Table 2. Irritable Bowel Syndrome Symptoms Symptom Severity Score and Bowel Habit (Bristol Stool Form scale) in the Intervention Groups

	Low-FODMAP diet			Traditional IBS diet			*P* value between intervention groups[a]
	Baseline (n = 33), mean ± SD	Intervention (n = 33), mean ± SD	*P* value within group[a]	Baseline (n = 34), mean ± SD	Intervention (n = 34), mean ± SD	*P* value within group[a]	
IBS-SSS total score	324 ± 69	246 ± 127	*<.001*	302 ± 61	236 ± 78	*<.001*	.62
Abdominal pain intensity	51.8 ± 23.8	42.2 ± 32.6	.07	46.9 ± 23.0	37.6 ± 26.9	.06	.53
Abdominal pain frequency	*57.6 ± 31.4*	*43.6 ± 30.6*	*.008*	*60.6 ± 28.6*	*37.8 ± 26.5*	*<.001*	.33
Abdominal distension	*68.7 ± 21.6*	*45.8 ± 32.8*	*<.001*	*62.4 ± 26.2*	*50.0 ± 31.5*	*.003*	.60
Dissatisfaction of bowel habit	65.9 ± 25.5	58.5 ± 31.2	.22	*63.6 ± 21.5*	*53.4 ± 25.3*	*.01*	.47
Interference on life in general	*72.5 ± 20.7*	*55.9 ± 31.0*	*.001*	*69.9 ± 20.8*	*58.6 ± 24.3*	*.002*	.69
Stool consistency	4.0 ± 1.1	3.9 ± 1.1	.12	3.8 ± 1.1	3.6 ± 1.0	.07	.28
Stool frequency	*1.9 ± 0.8*	*1.5 ± 0.7*	*<.001*	1.6 ± 0.7	1.5 ± 0.6	.15	.64

NOTE. Significant differences are displayed in italic.
[a]Comparisons were made per protocol, that is, in participants who completed the intervention.

To conclude, this is the first trial using an active comparator to a low-FODMAP diet in a randomized, controlled, single-blinded trial, with the attempt to resemble clinical practice. Both a low-FODMAP diet and a traditional IBS diet improved IBS symptoms, without any clear differences between the 2 strategies. Future studies should aim to further improve strategies for providing dietary advice to patients with IBS, potentially combining elements from different strategies and ideally customizing dietary advice for different patient populations. Monitoring calorie and nutrient intakes in patients who follow dietary advice seems to be important.

EDITORIALS

Are Proton Pump Inhibitors Affecting Intestinal Microbiota Health?

Gastroenterology 2015;149:952–957

Longer Withdrawal Time Is Associated With a Reduced Incidence of Interval Cancer After Screening Colonoscopy

Aasma Shaukat,[1,2,3] Thomas S. Rector,[3] Timothy R. Church,[4] Frank A. Lederle,[3] Adam S. Kim,[5] Jeffery M. Rank,[5] and John I. Allen[6]

[1]Division of Gastroenterology, Minneapolis Veterans Affairs Health Care System, Minneapolis, Minnesota; [2]Department of Medicine, University of Minnesota School of Medicine, Minneapolis, Minnesota; [3]Center for Chronic Disease Outcomes Research, Minneapolis Veterans Affairs Health Care System, Minneapolis, Minnesota; [4]Division of Environmental Health Sciences, School of Public Health, University of Minnesota, Minneapolis, Minnesota; [5]Minnesota Gastroenterology P.A., St. Paul, Minnesota; and [6]Department of Medicine, Yale University School of Medicine, New Haven, Connecticut

BACKGROUND & AIMS: Withdrawal times and adenoma detection rates are widely used quality indicators for screening colonoscopy. More rapid withdrawal times have been associated with undetected adenomas, which can increase risk for interval colorectal cancer. **METHODS:** We analyzed records of 76,810 screening colonoscopies performed between 2004 and 2009, by 51 gastroenterologists practicing in Minneapolis and St Paul, MN. Colonoscopy records were linked electronically to the state cancer registry (Minnesota Cancer Surveillance System) to identify incident interval cancers that were diagnosed within 5.5 years after the screening examination. **RESULTS:** The physicians' mean ± SD withdrawal time was 8.6 ± 1.7 minutes and adenoma detection rates were 25% ± 9%. Longer mean withdrawal times were associated with higher adenoma detection rates (3.6% per minute; 95% confidence interval: 2.4% to 4.8%; $P < .0001$). We identified 78 cancers during 410,687 person-years of follow-up, for an annual rate of 0.19/1000 person-years. Physicians' mean annual withdrawal times were inversely associated with cancer incidence ($P < .0001$). Compared with withdrawal times ≥6 minutes, the adjusted incidence rate ratio for withdrawal times of <6 minutes was 2.3 (95% confidence interval: 1.5–3.4; $P < .0001$). **CONCLUSIONS:** Shorter mean annual withdrawal times during screening colonoscopies were independently associated with lower adenoma detection rates and increased risk of interval colorectal cancer.

Gastroenterology 2015;149:883–885

BRIEF REPORTS

Proton Pump Inhibitors Alter Specific Taxa in the Human Gastrointestinal Microbiome: A Crossover Trial

Daniel E. Freedberg,[1] Nora C. Toussaint,[2] Sway P. Chen,[3] Adam J. Ratner,[4] Susan Whittier,[5] Timothy C. Wang,[1] Harris H. Wang,[5,6,§] and Julian A. Abrams[1,§]

We conducted an open-label crossover trial to test whether proton pump inhibitors (PPIs) affect the gastrointestinal microbiome to facilitate *Clostridium difficile* infection (CDI). Twelve healthy volunteers each donated 2 baseline fecal samples, 4 weeks apart (at weeks 0 and 4). They then took PPIs for 4 weeks (40 mg omeprazole, twice daily) and fecal samples were collected at week 8. Six individuals took the PPIs for an additional 4 weeks (from week 8 to 12) and fecal samples were collected from all subjects at week 12. Samples were analyzed by 16S ribosomal RNA gene sequencing. We found no significant within-individual difference in microbiome diversity when we compared changes during baseline vs changes on PPIs. There were, however, significant changes during PPI use in taxa associated with CDI (increased Enterococcaceae and Streptococcaceae, decreased Clostridiales) and taxa associated with gastrointestinal bacterial overgrowth (increased Micrococcaceae and Staphylococcaceae). In a functional analysis, there were no changes in bile acids on PPIs, but there was an increase in genes involved in bacterial invasion. These alterations could provide a mechanism by which PPIs predispose to CDI. ClinicalTrials.gov ID NCT01901276.

Gastroenterology 2015;149:938–951

Physician Non-adherence to Colonoscopy Interval Guidelines in the Veterans Affairs Healthcare System

Marcus R. Johnson,[1,2] Janet Grubber,[2] Steven C. Grambow,[1,3] Matthew L. Maciejewski,[1,4] Tyra Dunn-Thomas,[2] Dawn Provenzale,[1,2,5] and Deborah A. Fisher[2,5]

[1]Cooperative Studies Program Epidemiology Center-Durham, Durham Veterans Affairs Medical Center, Durham, North Carolina; [2]Center for Health Services Research in Primary Care, Durham Veterans Affairs Medical Center, Durham, North Carolina; [3]Department of Biostatistics and Bioinformatics, Duke University, Durham, North Carolina; [4]Division of General Internal Medicine, Department of Medicine, Duke University Medical Center, Durham, North Carolina; and [5]Division of Gastroenterology, Department of Medicine, Duke University Medical Center, Durham, North Carolina

BACKGROUND & AIMS: Colonoscopy can decrease colorectal cancer (CRC) mortality, although performing this procedure more frequently than recommended could increase costs and risks to patients. We aimed to determine rates and correlates of physician non-adherence to guidelines for repeat colonoscopy screening and polyp surveillance intervals. **METHODS:** We performed a multi-center, retrospective, observational study using administrative claims, physician databases, and electronic medical records (EMR) from 1455 patients (50–64 y old) who underwent colonoscopy in the Veterans Affairs healthcare system in fiscal year 2008. Patients had no prior diagnosis of CRC or inflammatory bowel disease, and had not undergone colonoscopy examinations in the previous 10 years. We compared EMR-documented, endoscopist-recommended intervals for colonoscopies with intervals recommended by the 2008 Multi-Society Task Force guidelines. **RESULTS:** The overall rate of non-adherence to guideline recommendations was 36% and ranged from 3% to 80% among facilities. Non-adherence was 28% for patients who underwent normal colonoscopies, but 45%–52% after colonoscopies that identified hyperplastic or adenomatous polyps. Most of all recommendations that were not followed recommended a shorter surveillance interval. In adjusted analyses, non-adherence was significantly higher for patients whose colonoscopies identified hyperplastic (odds ratio [OR] = 3.1; 95% CI, 1.7–5.5) or high-risk adenomatous polyps (OR = 3.0; 95% CI, 1.2–8.0), compared to patients with normal colonoscopy examinations, but not for patients with low-risk adenomatous polyps (OR = 1.8; 95% CI, 0.9–3.7). Non-adherence was also associated with bowel preparation quality, geographic region, Charlson comorbidity score, and colonoscopy indication. **CONCLUSIONS:** In a managed care setting with salaried physicians, endoscopists recommend repeat colonoscopy sooner than guidelines for more than one third of patients. Factors associated with non-adherence to guideline recommendations were colonoscopy findings, quality of bowel preparation, and geographic region. Targeting endoscopist about non-adherence to colonoscopy guidelines could reduce overuse of colonoscopy and associated healthcare costs.

Gastroenterology 2015;149:907–917

Identification of Patients With Variants in *TPMT* and Dose Reduction Reduces Hematologic Events During Thiopurine Treatment of Inflammatory Bowel Disease

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BACKGROUND & AIMS: More than 20% of patients with inflammatory bowel disease (IBD) discontinue thiopurine therapy because of severe adverse drug reactions (ADRs); leukopenia is one of the most serious ADRs. Variants in the gene encoding thiopurine S-methyltransferase (TPMT) alter its enzymatic activity, resulting in higher levels of thiopurine metabolites, which can cause leukopenia. We performed a prospective study to determine whether genotype analysis of *TPMT* before thiopurine treatment, and dose selection based on the results, affects the outcomes of patients with IBD. **METHODS:** In a study performed at 30 Dutch hospitals, patients were assigned randomly to groups that received standard treatment (control) or pretreatment screening (intervention) for 3 common variants of *TPMT* (*TPMT**2, *TPMT**3A, and *TPMT**3C). Patients in the intervention group found to be heterozygous carriers of a variant received 50% of the standard dose of thiopurine (azathioprine or 6-mercaptopurine), and patients homozygous for a variant received 0%–10% of the standard dose. We compared, in an intention-to-treat analysis, outcomes of the intervention (n = 405) and control groups (n = 378) after 20 weeks of treatment. Primary outcomes were the occurrence of hematologic ADRs (leukocyte count $< 3.0*10^9$/L or reduced platelet count $< 100*10^9$/L) and disease activity (based on the Harvey–Bradshaw Index for Crohn's disease [n = 356] or the partial Mayo score for ulcerative colitis [n = 253]). **RESULTS:** Similar proportions of patients in the intervention and control groups developed a hematologic ADR (7.4% vs 7.9%; relative risk, 0.93; 95% confidence interval, 0.57–1.52) in the 20 weeks of follow-up evaluation; the groups also had similar mean levels of disease activity ($P = .18$ for Crohn's disease and $P = .14$ for ulcerative colitis). However, a significantly smaller proportion of carriers of the *TPMT* variants in the intervention group (2.6%) terval, 0.01–0.85). **CONCLUSIONS:** Screening for variants in *TPMT* did not reduce the proportions of patients with hematologic ADRs during thiopurine treatment for IBD. However, there was a 10-fold reduction in hematologic ADRs among variant carriers who were identified and received a dose reduction, compared with variant carriers who did not, without differences in treatment efficacy. ClinicalTrials.gov number: NCT00521950.

COVERING THE COVER

Anson W. Lowe and Richard H. Moseley, Section Editors

Increased Autoimmunity in Nonceliac Wheat Sensitivity Compared With Irritable Bowel Syndrome

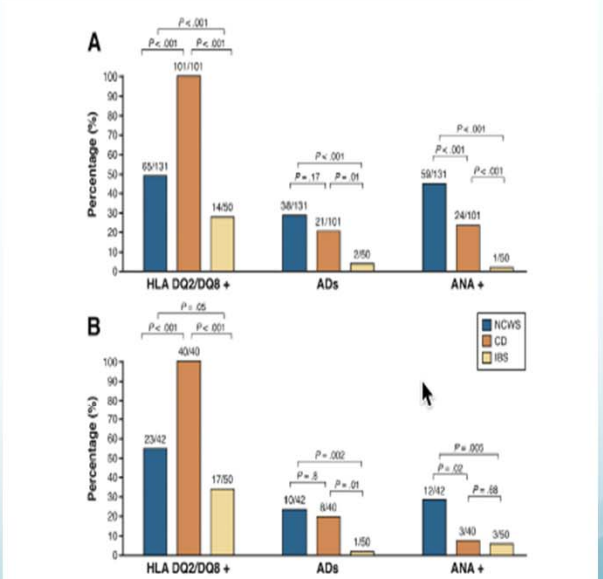

Figure 1. Frequency of HLA haplotypes DQ2 and/or DQ8, positive serum antinuclear antibodies (ANA) and autoimmune diseases in 131 nonceliac wheat-sensitive (NCWS) patients, 101 celiac disease (CD) controls, and 50 irritable bowel syndrome (IBS) controls, included in the retrospective study (*A*) and in 42 NCWS patients, 40 CD, and 50 irritable bowel syndrome (IBS) controls included in the prospective study (*B*).

Question

- A 36 yr M is seen in the office. He complains of gas, bloating, occasional loose stools and diffuse abdominal pain. He has had previous negative investigations including UGI biopsies negative for celiac disease. He says he feels better if he avoids gluten. Do you:
- A) do bloodwork for celiac disease
- B) do other bloodwork
- D) do other tests
- E) tell him to continue a gluten free diet

Gastroenterology 2015;149:596–603

High Proportions of People With Nonceliac Wheat Sensitivity Have Autoimmune Disease or Antinuclear Antibodies

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BACKGROUND & AIMS: There is much interest in wheat sensitivity among people without celiac disease (CD), but little is known about any risks associated with the condition. We evaluated the prevalence of autoimmune diseases (ADs) among patients with nonceliac wheat sensitivity (NCWS), and investigated whether they carry antinuclear antibodies (ANA). **METHODS:** We performed a retrospective study of 131 patients diagnosed with NCWS (121 female; mean age, 29.1 years) at 2 hospitals in Italy from January 2001 through June 2011. Data were also collected from 151 patients with CD or irritable bowel syndrome (IBS) (controls). Patient medical records were reviewed to identify those with ADs. We also performed a prospective study of 42 patients (38 female; mean age, 34 years) diagnosed with NCWS from July 2011 through March 2014 at 3 hospitals in Italy. One hundred age- and sex-matched subjects with CD or IBS served as controls. Serum samples were collected from all subjects and ANA levels were measured by immunofluorescence analysis. Participants completed a questionnaire and their medical records were reviewed to identify those with ADs. **RESULTS:** In the retrospective analysis, similar portions of subjects with NCWS (29%) and CD (29%) developed ADs (mainly Hashimoto's thyroiditis, 29 cases), compared with a smaller proportion of subjects with IBS (4%) ($P < .001$). In the prospective study, 24% of subjects with NCWS, 20% of subjects with CD, and 2% of subjects with IBS developed ADs ($P < .001$). In the retrospective study, serum samples tested positive for ANA in 46% of subjects with NCWS (median titer, 1:80), 24% of subjects with CD ($P < .001$), and 2% of subjects IBS ($P < .001$); in the prospective study, serum samples were positive for ANA in 28% of subjects with NCWS, 7.5% of subjects with CD ($P = .02$), and 6% of subjects with IBS ($P = .005$ vs patients with NCWS). ANA positivity was associated with the presence of the HLA DQ2/DQ8 haplotypes ($P < .001$). **CONCLUSIONS:** Higher proportions of patients with NCWS or CD develop autoimmune disorders, are ANA positive, and showed DQ2/DQ8 haplotypes compared with patients with IBS.

Question

- A 76 yr M is seen in ER with melena and hematemesis. He is on Dabigatran. He is not on a PPI.
- A) on d/c should he be given a PPI if he stays on Dabigatran
- B) you call for the Dabigatran reversal agent
- C) you keep your fingers crossed and wait until you can do an EGD

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Prevention of Dabigatran-Related Gastrointestinal Bleeding With Gastroprotective Agents: A Population-Based Study

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BACKGROUND & AIMS: Use of dabigatran, an inhibitor of thrombin, increases the risk of gastrointestinal bleeding (GIB). However, it is not clear whether gastroprotective agents (GPAs) prevent GIB in dabigatran users. We investigated the risk of GIB and the role of gastroprotective agents (including proton pump inhibitors and histamine type-2–receptor antagonists) in patients using dabigatran. **METHODS:** We performed a retrospective cohort study using a population-wide database managed by the Hong Kong Hospital Authority. Patients newly prescribed dabigatran from 2010 through 2013 were included in the analysis. Poisson regression was used to assess the risk of GIB in dabigatran users by incidence rate ratio (IRR), adjusted for patient characteristics, comorbidities, and concurrent medications. **RESULTS:** Among the 5041 patients newly prescribed dabigatran, 124 (2.5%) developed GIB during follow-up evaluation (4.2/100 patient-years). The risk of GIB in this population increased among patients 75 years and older (IRR, 2.47; 95% confidence interval [CI], 1.66–3.68), patients with a history of peptic ulcers or GIB (IRR, 2.31; 95% CI, 1.54–3.46), and patients who used aspirin (IRR, 1.52; 95% CI, 1.03–2.24). Concomitant use of gastroprotective agents was associated with a reduced risk of GIB (IRR, 0.52; 95% CI, 0.35–0.77). Subcategory analysis showed that use of proton pump inhibitors (IRR, 0.53; 95% CI, 0.31–0.91) or histamine type-2–receptor antagonists (IRR, 0.61; 95% CI, 0.40–0.94) were associated with a lower risk of GIB. Further analysis showed that the risk reduction by gastroprotective agents was significant for only upper GIB (IRR, 0.29; 95% CI, 0.15–0.54), and only for patients with a prior history of peptic ulcers or GIB (IRR, 0.14; 95% CI, 0.06–0.30). **CONCLUSIONS:** In the Hong Kong population, use of gastroprotective agents was associated with a reduced risk of GIB in patients taking dabigatran. The association was stronger for upper GIB than lower GIB, and in patients with a prior history of peptic ulcers or GIB.

19 October 2015

FDA Approves Praxbind® (idarucizumab), Specific Reversal Agent for Pradaxa® (dabigatran etexilate)

For Media outside of the US

- First FDA approval of a specific reversal agent for a novel oral anticoagulant (NOAC)[1]
- Praxbind® immediately reverses the anticoagulant action of dabigatran [2,3]

Ingelheim, Germany, 19. October 2015 – Boehringer Ingelheim GmbH announced the U.S. Food and Drug Administration (FDA) granted approval of Praxbind® (idarucizumab).[4] Praxbind® is indicated for patients treated with Pradaxa® (dabigatran etexilate), when reversal of the anticoagulant effects of dabigatran is needed for emergency surgery/urgent procedures or in life-threatening or uncontrolled bleeding.[1]

Idarucizumab filed with EMA and Health Canada as Antidote for Dabigatran-Boehringer - 04-Mar-2015

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Year - 2013

Boehringer has submitted BI 655075 (idarucizumab) for approval of marketing authorisation to the European Medicines Agency (EMA) and Health Canada, for use in patients who require rapid reversal of the anticoagulant effect of dabigatran, the active ingredient in Pradaxa. This follows filing with the FDA. The submissions are based on the results from clinical trials of idarucizumab in volunteers, including elderly and renally impaired individuals. Phase I data showed an immediate, complete and sustained reversal of the anticoagulant effect of dabigatran following the administration of idarucizumab and no pro-thrombotic effect. The submissions also include first interim data from the ongoing RE-VERSE ADTM study. RE-VERSE ADTM is an ongoing global Phase III patient study in which Boehringer Ingelheim continues to evaluate idarucizumab in patients treated with Pradaxa who are in need of emergency intervention, or experience an uncontrolled or life-threatening bleeding event.

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Pouch Inflammation Is Associated With a Decrease in Specific Bacterial Taxa

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BACKGROUND & AIMS: Pouchitis is a common long-term complication in patients with ulcerative colitis (UC) undergoing proctocolectomy with ileal pouch-anal anastomosis. Because the inflammation occurs in a previously normal small bowel, studies of this process might provide information about the development of Crohn's disease. Little is known about the intestinal microbiome of patients with pouchitis. We investigated whether specific bacterial populations correlate with the pouch disease phenotype and inflammatory activity. **METHODS:** We performed a prospective study of patients with UC who underwent pouch surgery (N = 131) from 1981 through 2012 and were followed at Tel Aviv Medical Center. Patients were assigned to groups based on their degree and type of pouch inflammation. Patients with familial adenomatous polyposis after pouch surgery (n = 9), individuals with intact colons undergoing surveillance colonoscopy (n = 10), and patients with UC who did not undergo surgery (n = 9) served as controls. We collected demographic and disease activity data (based on the Pouchitis Disease Activity Index) and measured levels of C-reactive protein. Fecal samples were collected, levels of calprotectin were measured, and microbiota were analyzed by 16S ribosomal RNA gene amplicon pyrosequencing. **RESULTS:** Increased proportions of the *Fusobacteriaceae* family correlated with increased disease activity and levels of C-reactive protein in patients with UC who underwent pouch surgery. In contrast, proportions of *Faecalibacterium* were reduced in patients with pouchitis vs controls; there was a negative correlation between proportion of *Faecalibacterium* and level of C-reactive protein. There was an association between antibiotic treatment, but not biologic or immunomodulatory therapy, with reduced proportions of 11 genera and with increased proportions of *Enterococcus* and *Enterobacteriaceae*. **CONCLUSIONS:** Reductions in protective bacteria and increases in inflammatory bacteria are associated with pouch inflammation in patients with UC who underwent pouch surgery. The finding that antibiotics exacerbate dysbiosis indicates that these drugs might not provide long-term benefit for patients with pouchitis. Additional studies of this form of dysbiosis could provide information about the pathogenesis of Crohn's disease.

Thank you

- Please remember to complete your online evaluation