RAPID FIRE CASES
CDDW 2017
MARCH 6TH 2017
Laura Targownik
Associate Professor of Medicine
University of Manitoba
Case #1: Management of Post-Operative CD

- 36 y.o female
  - Diagnosed with ileocolonic Crohn’s Disease 10 years ago
  - On long term AZA
  - Smokes 10 cigarettes/day
  - 6 months ago:
    - Presents with obstructive symptoms, evidence of fibrotic stricture on MRI and colonoscopy
    - No response to 3 doses IFX, undergoes ileal resection and ileocecal reanastomosis
    - Now being seen 1 month post discharge
Case #1: Management of Post-Operative CD

Question 1:
- Should you:
  A) Start Metronidazole
  B) Continue IFX at maintenance dose
  C) Continue AZA monotherapy
  D) Observe without therapy

Question 2:
- You should monitor response to therapy based on:
  A) Symptoms Alone
  B) Endoscopy if symptoms develop
  C) Endoscopy at 6-12 months if no therapy used
  D) Endoscopy at 6-12 months for all persons
Rutgeerts’ Scoring System

Image from Regueiro et al, Gastroenterology 2017;152:277–295
RCT of IFX 5mg/kg q8w vs placebo, up to 104 weeks f/u

Primary Outcome:
- Clinical recurrence at w78

Secondary Outcome
- Endoscopic Recurrence at or prior to w78
Post-Operative Crohn’s Endoscopic Recurrence Trial (POCER)

- Assessed role for standard colonoscopy at 6 months following resection to guide therapy

- At 18 months, endoscopic recurrence rate ≥2 or greater
  - 49% active therapy
  - 67% standard therapy
  - P = 0.03
High risk patient
- Diagnosed at age 30
- smoker
- ≥2 resections
Case #1: Management of Post-Operative CD

Question 1:
- Should you:
  A) Start Metronidazole
  B) Continue IFX at maintenance dose
  C) Continue AZA monotherapy
  D) Observe without therapy

Question 2:
- You should monitor response to therapy based on:
  A) Symptoms Alone
  B) Endoscopy if symptoms develop
  C) Endoscopy at 6-12 months if no therapy used
  D) Endoscopy at 6-12 months for all persons
Case #2: Ustekinumab in Crohn’s Disease

- 25 y.o male with ileocolonic Crohn’s disease x 18 months
- Started IFX 5mg/kg + AZA 6 months ago
  - Initial response, but now once again symptomatic,
  - No response to 2 course
- Recent MRI shows active inflammation in ascending colon, cecum, and terminal ileum, Hgb 105, CRP 25
- Trough IFX level: 7.6, no response to increase in IFX to 10mg/kg q6w
- You have decided to institute Ustekinumab as a second line agent
Case #2: Ustekinumab in Crohn’s Disease

Question 3: What will you tell this patient that the likelihood of clinical remission at 8 weeks following 1 dose of UST
A) ~15%
B) ~35%
C) ~50%
D) ~65%

Question 4: Assuming a clinical response at week 8, what is the likelihood of being in remission at the end of the year?
A) ~20%
B) ~30%
C) ~40%
D) ~50%
Case #2: Ustekinumab in CD

- Ustekinumab:
  - Monoclonal antibody to p40 subunit of IL-12 and IL-23 Leads to decrease in $T_H1$ and $T_{H-17}$ activity

Image from Teng MW et al, Nat Med. 2015 Jul;21(7):719-29
Reports results of 3 linked RCTs:

- UNITI 1: Induction of Remission in CD in Anti-TNF Failures
- UNITI 2: Induction of Remission in CD in Anti-TNF Naïve Patients
- UNITI-IM: Maintenance Therapy for CD up to 44 weeks
UNITI 1 and 2:
- Randomized to *intravenous*
  - Placebo
  - 130mg UST
  - 260-520mg UST, dependent of weight
- Assessed for clinical response at 8 weeks

UNITI IM
- Responders at 8 weeks randomized to *subcutaneous*
  - UST 90mg q8w
  - UST 90mg q12w
  - Placebo
- Non-responders at 8 weeks given open label sc UST
A Clinical Response

UNITI-1

UNITI-2

B Clinical Remission

UNITI-1

UNITI-2

Case #2: Ustekinumab in CD

- Among non-randomized subjects in UNITI-IM
  - $\frac{1}{2}$ in clinical remission at 1 year
  - $\frac{2}{3}$ with clinical response at 1 year

- Overall
  - No endoscopic outcomes
  - No difference between IM users and non-IM users
  - Low rate of antibody development

- UST now approved in Canada
  - 6mg/kg dose for induction
  - 90mg q8w sc dosing for maintenance
Case #2: Ustekinumab in CD

Question 3: What will you tell this patient that the likelihood of clinical response at 8 weeks following 1 dose of UST
A) ~15%
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C) ~50%
D) ~65%

Question 4: Assuming a clinical response at week 8, what is the likelihood of being in remission at the end of the year?
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B) ~30%
C) ~40%
D) ~50%
Case #3: Dysplasia Surveillance in UC

- 41 y.o male with history of proctosigmoiditis to 20cm
- Most recent colonoscopy 3 years ago
  - Mayo 2 inflammation in rectum and distal sigmoid
  - No histologic or endoscopic inflammation proximally
- You have decided to perform endoscopic dysplasia surveillance
Case #3: Dysplasia Surveillance in UC

- **Question 5**: How would you survey for dysplasia in this patient?

  A) Standard endoscopy with targeted biopsies + random biopsies throughout colon
  
  B) Standard endoscopy with targeted biopsies + random biopsies from affected areas of the colon
  
  C) Standard endoscopy with only targeted biopsies of suspicious lesions
  
  D) Enhanced endoscopy (high definition or dye augmented), targeted biopsies + random biopsies throughout colon
  
  E) Enhanced endoscopy (high definition or dye augmented) + targeted biopsies, random biopsies from affected areas only
  
  F) Enhanced endoscopy (high definition or dye augmented), targeted biopsies + no random biopsies
RCT comparing
- HD Colonoscopy with only targeted biopsies of visible lesions
- HD Colonoscopy with targeted and random biopsies (4 Bx q 10cm)

All patients with UC > 7 years

Assessed
- Proportion with dysplasia
- Proportion of biopsies with dysplasia
- Relative proportions of dysplasia detected via targeted vs random biopsies
- Procedure Time
- Random biopsies:
  - 13/2747 (0.5%) of inflamed or previous inflamed tissue
  - 0/707 in non-inflamed tissue

- RR for discovery of dysplasia: 1.25 (0.68-2.31)

- Avoiding random biopsies reduced procedure time by 50%
At time of SCENIC meeting in 2014
- 30% of panel felt unnecessary if WLE used
- 60% felt unnecessary if chromoendoscopy was used

<table>
<thead>
<tr>
<th></th>
<th># of Studies/# of patients</th>
<th>% with dysplasia on targeted biopsies</th>
<th>% with dysplasia found only on random biopsies</th>
<th>% of all patients with dysplasia detected only by random Bx</th>
<th>Rate of +ve random biopsies per all biopsies taken</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chromoendoscopy</td>
<td>7 / 1289</td>
<td>12.4%</td>
<td>1.2%</td>
<td>90.2%</td>
<td>0.1%</td>
</tr>
<tr>
<td>HD WLE</td>
<td>4/ 382</td>
<td>15.4%</td>
<td>1.6%</td>
<td>90.6%</td>
<td>0.2%</td>
</tr>
<tr>
<td>SD WLE</td>
<td>11 / 1785</td>
<td>11.8%</td>
<td>2.6%</td>
<td>80.4%</td>
<td>0.1%</td>
</tr>
</tbody>
</table>
Case #3: Dysplasia Surveillance in UC

Question 5: How would you survey for dysplasia in this patient?

A) Standard endoscopy with targeted biopsies + random biopsies throughout colon

B) Standard endoscopy with targeted biopsies + random biopsies from affected areas of the colon

C) Standard endoscopy with only targeted biopsies of suspicious lesions

D) Enhanced endoscopy (high definition or dye augmented), targeted biopsies + random biopsies throughout colon

E) Enhanced endoscopy (high definition or dye augmented) + targeted biopsies, random biopsies from affected areas only

F) Enhanced endoscopy (high definition or dye augmented), targeted biopsies + no random biopsies
Case #4: Use of Rifaxamin in IBS-D

- 29 y.o female
  - 5 year history of IBS-D
  - Over last 3 months, has had increasing symptom burden
  - Was given rifaxamin at walk-in clinic
    - Felt better for about a month
    - Now back to usual symptoms
Case #4: Use of Rifaximin in IBS-D

Question 6: Do you use Rifaxamin to treat symptoms of IBS-D?

A) Yes
B) No

Question 7: What would be the anticipated improvement in short term response rate over placebo

A) 5-10%
B) 10-15%
C) 15-20%
D) >20%
Original RCT evaluating Rifaxaxmin

Adequate relief of IBS-D and IBS-A achieved in over 2 of next 4 weeks following treatment in:
- RIF: 41%
- Pla: 32%

Approx. 1/3 of responders lose response over the next 2 months
RCT of retreatment with RIF for persons who
- Had response to open label RIF
- Relapsed within 18 weeks

Randomized to
- 2 weeks placebo
- 2 weeks of RIF 550 tid

Outcome
- % with adequate response of IBS
  - >=2 out of 4 weeks following completion of therapy with both
    - 30% reduction in abd. pain score from baseline
    - 50% reduction in number of days with loose stools
Repeat Treatment With Rifaximin Is Safe and Effective in Patients With Diarrhea-Predominant Irritable Bowel Syndrome


Open-label treatment phase
- Screening
- 7–13 days placebo
- 2 weeks rifaximin
- 4 weeks follow-up

Observation phase
- Responders followed; only patients with symptom relapse randomized
- Variable up to 18 weeks

Double-blind treatment phases
- First repeat treatment
- 2 weeks rifaximin
- 4 weeks follow-up
- 6 weeks
- Repeat treatment observation phase
- 2 weeks rifaximin
- 4 weeks follow-up
- 6 weeks
- Second repeat treatment
- 2 weeks placebo
- 4 weeks follow-up

Follow-up
- 4 weeks

Primary endpoint
- Durable Response
- Prevention of Recurrence

Randomize 1:1
Nonresponders withdrawn and proceeded to EOS

Study day 1

SC SC SC SC SC
Response rate over placebo: 6.6%

Overall numbers of recurrence prevention is low (13.2% after 2 courses of RIF)
Case #4: Use of Rifaxamin in IBS-D

Question 6: Do you use Rifaxamin to treat symptoms of IBS-D?

A) Yes
B) No

Question 7: What would be the anticipated improvement in short term response rate over placebo

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Rapid-Fire Case Presentations

Canadian Digestive Disease Week
Banff, AB
March 6, 2017

Philip M. Sherman, MD, FRCPC
Professor of Paediatrics, Microbiology, Nutritional Sciences, & Dentistry
Hospital for Sick Children, University of Toronto
Canada Research Chair in Gastrointestinal Disease
Disclosures

PMS has the following financial relationships to disclose:

*Lallemand Health Solutions (research contract)
*Abbott Nutrition (honorarium)
*Mead Johnson Nutrition (honorarium)
*Nestlé Nutrition (honorarium)
*Procter & Gamble (honorarium)
Antibe Therapeutics (stockholder)

* Products or services produced by this company are relevant to my presentation.
### CanMEDS Roles Covered

<table>
<thead>
<tr>
<th>Role</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Medical Expert</strong></td>
<td>Medical Experts, physicians integrate all of the CanMEDS Roles, applying medical knowledge, clinical skills, and professional values in their provision of high-quality and safe patient-centered care. Medical Expert is the central physician Role in the CanMEDS Framework and defines the physician’s clinical scope of practice.</td>
</tr>
<tr>
<td><strong>Communicator</strong></td>
<td>Communicators, physicians form relationships with patients and their families that facilitate the gathering and sharing of essential information for effective health care.</td>
</tr>
<tr>
<td><strong>Collaborator</strong></td>
<td>Collaborators, physicians work effectively with other health care professionals to provide safe, high-quality, patient-centred care.</td>
</tr>
<tr>
<td><strong>Leader</strong></td>
<td>Leaders, physicians engage with others to contribute to a vision of a high-quality health care system and take responsibility for the delivery of excellent patient care through their activities as clinicians, administrators, scholars, or teachers.</td>
</tr>
<tr>
<td><strong>Health Advocate</strong></td>
<td>Health Advocates, physicians contribute their expertise and influence as they work with communities or patient populations to improve health. They work with those they serve to determine and understand needs, speak on behalf of others when required, and support the mobilization of resources to effect change.</td>
</tr>
<tr>
<td><strong>Scholar</strong></td>
<td>Scholars, physicians demonstrate a lifelong commitment to excellence in practice through continuous learning and by teaching others, evaluating evidence, and contributing to scholarship.</td>
</tr>
<tr>
<td><strong>Professional</strong></td>
<td>Professionals, physicians are committed to the health and well-being of individual patients and society through ethical practice, high personal standards of behaviour, accountability to the profession and society, physician-led regulation, and maintenance of personal health.</td>
</tr>
</tbody>
</table>
Learning objectives:

2. Decide whether these selected publications should have an impact on your clinical practice.
Case #1

30 yo F with new onset hematochezia
Brother died of brain tumour (glioma) as a teenager

What is the diagnosis:?

a) Lynch s.
b) Turcot’s s.
c) Biallelic mismatch repair
d) Neurofibromatosis
Biallelic Mismatch Repair Gene Deficiency Syndrome (BMMRD)

Biallelic mutations in the MMR genes: 

*PMS2, MSH6, MLH1, MSH2*

Novel cancer predisposition syndrome

PD-1 Blockade in Tumors with Mismatch-Repair Deficiency

Progression-free survival in cohorts with colorectal cancer

P<0.001 by log-rank test

Probability of Progression-free Survival

No. at Risk
Mismatch repair–deficient 11 8 6 2 0 0 0
Mismatch repair–proficient 21 2 1 0 0 0 0

Months
Clinical, Endoscopic, and Histologic Characteristics of Ipilimumab-Associated Colitis


Table 1. Patient, Clinical, and Ipilimumab-Colitis-Related Characteristics (N = 27)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex</td>
<td>21 (78%)</td>
</tr>
<tr>
<td>Age, y (mean ± standard deviation)</td>
<td>60 ± 12</td>
</tr>
<tr>
<td>Prostate cancer</td>
<td>16</td>
</tr>
<tr>
<td>Melanoma</td>
<td>11</td>
</tr>
<tr>
<td>Days before diarrhea onset (median)</td>
<td>37</td>
</tr>
<tr>
<td>Number of ipilimumab doses (median)</td>
<td>3</td>
</tr>
<tr>
<td>Dosage ipilimumab, 3 mg/kg</td>
<td>11</td>
</tr>
<tr>
<td>Dosage ipilimumab, 10 mg/kg</td>
<td>16</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>27 (100%)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>8 (30%)</td>
</tr>
<tr>
<td>Hematochezia</td>
<td>7 (26%)</td>
</tr>
<tr>
<td>Nausea/vomitus</td>
<td>6 (22%)</td>
</tr>
<tr>
<td>Fever</td>
<td>4 (15%)</td>
</tr>
<tr>
<td>Mucus in stool</td>
<td>1 (3%)</td>
</tr>
</tbody>
</table>
Review

Phenotypic and genotypic characterisation of biallelic mismatch repair deficiency (BMMR-D) syndrome

Carol A. Durno a,b,c,*, Philip M. Sherman c, Melyssa Aronson a, David Malkin d, Cynthia Hawkins e, Doua Bakry d, Eric Bouffet d, Steven Gallinger a, Aaron Pollett c, Brittany Campbell f, Uri Tabori d, International BMMRD Consortium

Eur J Cancer 2015;51:977-983
Case #2

51 yo Canadian arrives for screening colonoscopy
No family history of colon cancer
Refuses fecal immunochemical testing (too “icky”)

Who should get the informed consent?

a) Staff person performing the procedure
b) Trainee performing the procedure
c) Trained nurse practitioner
d) Delegated administrative staff
e) Any of the above
Patients should receive information in their own language and given an opportunity to ask questions.
Consent should be obtained by the person performing the procedure (but not trainees).
Written information about the procedure should be provided.
Consent should be obtained before entering the procedure room.

plus 6 more key points . . .
Expert opinions and scientific evidence for colonoscopy key performance indicators

Colin J Rees,\textsuperscript{1} Roisin Bevan,\textsuperscript{2} Katharina Zimmermann-Fraedrich,\textsuperscript{3} Matthew D Rutter,\textsuperscript{2} Douglas Rex,\textsuperscript{4} Evelien Dekker,\textsuperscript{5} Thierry Ponchon,\textsuperscript{6} Michael Bretthauer,\textsuperscript{7} Jaroslaw Regula,\textsuperscript{8} Brian Saunders,\textsuperscript{9} Cesare Hassan,\textsuperscript{10} Michael J Bourke,\textsuperscript{11} Thomas Rösch\textsuperscript{3}

Cecal intubation rate
Adenoma detection rate
Bowel preparation
Rectal retroflexion
Withdrawal times
Sedation practices
Numbers
Polyp removal, retrieval, and histology
Case #3

33 yo F with refractory iron deficiency anemia
No GI symptoms
Family history of IBS
PE: pallor
otherwise negative
Laboratory: Hemoglobin 97 g/L; MCV
Albumin 33 g/L
anti-TTG 1 in 100

Next steps?:
a) Gluten free diet
b) Microbiome analysis
c) HLA DQ2/DQ8 status
d) EGD and biopsies
e) other
The Celiac Iceberg

Symptomatic Celiac Disease

Silent Celiac Disease

Latent Celiac Disease

Manifest mucosal lesion

Normal Mucosa

Genetic susceptibility: - DQ2, DQ8
Positive serology

What is a normal intestinal mucosa?
M Marsh & K Rostami Gastroenterology 2016;151:744-788
Clinical and Immunologic Features of Ultra-Short Celiac Disease

Peter D. Mooney, Matthew Kurien, Kate E. Evans, Eleanor Rosario, Simon S. Cross, Patricia Vergani, Marios Hadjivassiliou, Joseph A. Murray, and David S. Sanders

1 Academic Department of Gastroenterology, 2 Department of Histopathology, 3 Department of Neurology, Royal Hallamshire Hospital, Sheffield, United Kingdom; 4 University of Sheffield, Sheffield, United Kingdom; 5 Mayo Clinic, Rochester, Minnesota

Table 1. A Summary of the Available Studies Into Duodenal Bulb Biopsy Specimens for Diagnosing Celiac Disease

<table>
<thead>
<tr>
<th>Year/reference</th>
<th>Country</th>
<th>Adults/pediatrics</th>
<th>Patients, N</th>
<th>Celiac disease, n (%)</th>
<th>USCD, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2001[^10]</td>
<td>Austria</td>
<td>Adults</td>
<td>51</td>
<td>21 (41.2)</td>
<td>2 (9.5)</td>
</tr>
<tr>
<td>2004[^30]</td>
<td>Italy</td>
<td>Pediatrics</td>
<td>95</td>
<td>95 (100)</td>
<td>4 (4.2)</td>
</tr>
<tr>
<td>2005[^31]</td>
<td>Italy</td>
<td>Adults</td>
<td>1</td>
<td>1 (100)</td>
<td>1 (1.8)</td>
</tr>
<tr>
<td>2008[^8]</td>
<td>United Kingdom</td>
<td>Adults</td>
<td>56</td>
<td>56 (100)</td>
<td>1 (1.8)</td>
</tr>
<tr>
<td>2008[^32]</td>
<td>Italy</td>
<td>Pediatrics</td>
<td>1013</td>
<td>665 (65.6)</td>
<td>16 (2.4)</td>
</tr>
<tr>
<td>2009[^33]</td>
<td>Canada</td>
<td>Pediatrics</td>
<td>35</td>
<td>29 (81.6)</td>
<td>3 (11.4)</td>
</tr>
<tr>
<td>2010[^19]</td>
<td>United States</td>
<td>Pediatrics</td>
<td>198</td>
<td>198 (100)</td>
<td>10 (5.1)</td>
</tr>
<tr>
<td>2010[^34]</td>
<td>Italy</td>
<td>Pediatrics</td>
<td>47</td>
<td>42 (89.4)</td>
<td>5 (11.9)</td>
</tr>
<tr>
<td>2010[^9]</td>
<td>United States</td>
<td>Adults</td>
<td>80</td>
<td>40 (50)</td>
<td>5 (12.5)</td>
</tr>
<tr>
<td>2011[^35]</td>
<td>Israel</td>
<td>Pediatrics</td>
<td>87</td>
<td>87 (100)</td>
<td>6 (7.0)</td>
</tr>
<tr>
<td>2011[^12]</td>
<td>United Kingdom</td>
<td>Adults</td>
<td>376</td>
<td>126 (33.5)</td>
<td>11 (9.0)</td>
</tr>
<tr>
<td>2012[^11]</td>
<td>United Kingdom</td>
<td>Adults</td>
<td>77</td>
<td>28 (36.4)</td>
<td>5 (17.9)</td>
</tr>
<tr>
<td>2013[^38]</td>
<td>Australia</td>
<td>Pediatrics</td>
<td>101</td>
<td>101 (100)</td>
<td>8 (7.92)</td>
</tr>
<tr>
<td>2014[^13]</td>
<td>Italy</td>
<td>Adults</td>
<td>42</td>
<td>25 (59.5)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

“bulb biopsies finally reaffirmed in celiac disease diagnosis”
Case #4

44 yo M from Lebanon with dyspepsia and anxiety
Family history: + gastric cancer
PEx: negative
Laboratory: positive *H. pylori* serology, positive UBT, positive silver stain:
Prior courses of treatment: PPI alone, PMC, PAC, and PAC plus probiotics

Referred to you for treatment:
A) Sequential therapy
B) Quadruple therapy
C) Triple therapy with tetracycline
D) Monitor clinical course off treatment
Association Between *Helicobacter pylori* Eradication and Gastric Cancer Incidence: A Systematic Review and Meta-analysis

Yi-Chia Lee, Tsung-Hsien Chiang, Chu-Kuang Chou, Yu-Kang Tu, Wei-Chih Liao, Ming-Shiang Wu and David Y. Graham

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**Author**

**Incidence rate ratio (95% CI)**

**Percent, weight**

**Lowest tertile of incidence**

- Kosunen et al, 2011
  - 0.85 (0.43, 1.66)
  - 7.10
- Correa et al, 2000
  - 1.48 (0.25, 8.87)
- Wong et al, 2012
  - 3.04 (0.32, 9.16)
  - 0.63
- Lee et al, 2015
  - 0.94 (0.46, 1.90)
  - 6.48
- Yamaoka et al, 2009
  - 0.75 (0.30, 1.87)
  - 3.64
- Wong et al, 2004
  - 0.63 (0.25, 1.63)
  - 3.58
- Saito et al, 2005
  - 0.55 (0.08, 3.29)
  - 1.00
- Zhou et al, 2006
  - 0.29 (0.06, 1.38)
  - 1.50
- Subtotal (I-squared = 0.0%, P = .779)
  - 0.80 (0.56, 1.15)
  - 24.0%

**Intermediate tertile of incidence**

- You et al, 2006
  - 0.65 (0.42, 1.01)
  - 17.22
- Mabe et al, 2009
  - 0.49 (0.24, 0.99)
  - 3.32
- Takenaka et al, 2007
  - 0.23 (0.07, 0.75)
  - 2.28
- Take et al, 2007
  - 0.42 (0.13, 1.36)
  - 2.32
- Choi et al, 2014
  - 0.61 (0.28, 1.32)
  - 5.27
- Ogura et al, 2008
  - 0.35 (0.13, 0.91)
  - 3.44
- Nakagawa et al, 2006
  - 0.43 (0.21, 0.88)
  - 6.30
- Fukase et al, 2008
  - 0.38 (0.17, 0.81)
  - 5.48
- Subtotal (I-squared = 0.0%, P = .694)
  - 0.49 (0.36, 0.64)
  - 48.0%

**Highest tertile of incidence**

- Bao et al, 2014
  - 0.49 (0.20, 0.83)
  - 11.7
- Itohara et al, 1997
  - 0.09 (0.00, 1.54)
  - 0.39
- Kim et al, 2014
  - 0.27 (0.06, 1.19)
  - 1.40
- Shiotani et al, 2008
  - 1.23 (0.16, 9.69)
  - 0.75
- Kwon et al, 2014
  - 0.32 (0.13, 0.78)
  - 4.48
- Maehata et al, 2012
  - 0.59 (0.26, 1.35)
  - 5.63
- Saito et al, 2005
  - 0.13 (0.01, 2.36)
  - 0.37
- Seo et al, 2013
  - 0.42 (0.11, 1.69)
  - 1.67
- Subtotal (I-squared = 0.0%, P = .713)
  - 0.45 (0.32, 0.64)
  - 28.4%

**Overall (I-squared = 0.0%, P = .673)**

- 0.54 (0.46, 0.65)
  - 100%

**NOTE: weights are from random effects analysis**
The Toronto Consensus for the Treatment of *Helicobacter pylori* Infection in Adults


<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Concomitant</th>
<th>Sequential</th>
<th>Risk difference M-H, random, 95% CI</th>
<th>Risk difference M-H, random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events Total Weight</td>
<td></td>
</tr>
<tr>
<td>5.3.3 10 days</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ang TL 2015</td>
<td>125</td>
<td>153</td>
<td>130 154 9.4%</td>
<td>-0.03 [-0.11, 0.06]</td>
</tr>
<tr>
<td>Apostolopoulos P 2013</td>
<td>29</td>
<td>33</td>
<td>19 30 2.0%</td>
<td>0.25 [0.04, 0.45]</td>
</tr>
<tr>
<td>Area RD 2015</td>
<td>121</td>
<td>136</td>
<td>108 139 8.9%</td>
<td>0.11 [0.03, 0.20]</td>
</tr>
<tr>
<td>Huang YK 2012</td>
<td>74</td>
<td>84</td>
<td>68 85 6.2%</td>
<td>0.08 [-0.03, 0.19]</td>
</tr>
<tr>
<td>Kalapothakos P 2013</td>
<td>88</td>
<td>102</td>
<td>87 102 7.7%</td>
<td>0.01 [-0.09, 0.11]</td>
</tr>
<tr>
<td>Kim J 2014</td>
<td>52</td>
<td>65</td>
<td>49 72 3.8%</td>
<td>0.12 [-0.03, 0.26]</td>
</tr>
<tr>
<td>Kim SY 2014a</td>
<td>118</td>
<td>125</td>
<td>157 191 12.6%</td>
<td>0.12 [0.05, 0.19]</td>
</tr>
<tr>
<td>Kim SY 2014b</td>
<td>57</td>
<td>61</td>
<td>51 60 6.2%</td>
<td>0.08 [-0.03, 0.19]</td>
</tr>
<tr>
<td>McNicholl AG 2014a</td>
<td>146</td>
<td>168</td>
<td>138 170 10.4%</td>
<td>0.06 [-0.02, 0.14]</td>
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<tr>
<td>Ntoulis V 2014</td>
<td>99</td>
<td>108</td>
<td>97 104 8.5%</td>
<td>0.07 [-0.02, 0.16]</td>
</tr>
<tr>
<td>Wu DC 2010</td>
<td>107</td>
<td>115</td>
<td>108 117 12.7%</td>
<td>0.01 [-0.06, 0.07]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>1150</td>
<td>1224</td>
<td>68.4%</td>
<td>0.07 [0.03, 0.10]</td>
</tr>
<tr>
<td>Total events</td>
<td>1015</td>
<td>1002</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tau² = 0.00</td>
<td>Chiquadrado = 16.41; df = 10 (P = .09); I² = 30%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 3.53 (P = .0004)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

5.3.4 14 days

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Concomitant</th>
<th>Sequential</th>
<th>Risk difference M-H, random, 95% CI</th>
<th>Risk difference M-H, random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events Total Weight</td>
<td></td>
</tr>
<tr>
<td>Choi C 2012</td>
<td>32</td>
<td>36</td>
<td>23 27 2.9%</td>
<td>0.04 [-0.13, 0.21]</td>
</tr>
<tr>
<td>Lee S 2012</td>
<td>48</td>
<td>58</td>
<td>45 58 3.8%</td>
<td>0.05 [-0.06, 0.20]</td>
</tr>
<tr>
<td>Lim JH 2013</td>
<td>63</td>
<td>78</td>
<td>65 86 4.9%</td>
<td>0.05 [-0.07, 0.18]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>172</td>
<td>171</td>
<td>11.6%</td>
<td>0.05 [-0.03, 0.13]</td>
</tr>
<tr>
<td>Total events</td>
<td>143</td>
<td>133</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tau² = 0.00</td>
<td>Chiquadrado = 0.02; df = 2 (P = .99); I² = 0%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 1.14 (P = .25)</td>
<td></td>
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<td></td>
<td></td>
</tr>
</tbody>
</table>

Known local patterns?
- Low clarithromycin resistance OR
- High PPI triple therapy success rates

**Decision Tree**

- **PAMC**
  - If fails
    - **PBMT**
      - Consider optimized PBMT* (if fails)
        - **PAR**
          - If fails
            - **PBMT**
              - Consider optimized PBMT* (if fails)
                - **PAR**
                  - If fails
                    - **PBMT**
                      - Consider optimized PBMT* (if fails)
                        - **PAR**
                          - If fails
                            - **PAR**
                              - If fails
                                - **PAR**
                                  - If fails
                                    - **PAR**
Case #5: Surveillance of Sessile Serrated Adenoma

- 55 y.o male undergoing colonoscopic CRC screening, otherwise asymptomatic

- Found to have a 6mm sessile adenoma in the base of the cecum
  - Histology consistent with a sessile serrated adenoma

Image from Short et al, Am Fam Physician. 2015 Jan 15;91(2):93-100
Case #5: Surveillance of Sessile Serrated Adenoma

Question 8: When would you perform the next surveillance colonoscopy?

A) 1-2 years
B) ~ 3 years
C) ~ 5 years
D) ~ 10 years

Question 9: What is the risk of finding a metachronous high-risk lesion in the next 5 years?

A) 5-10%
B) 10-15%
C) 15-20%
D) >20%
Case #5: Surveillance of Sessile Serrated Adenoma

<table>
<thead>
<tr>
<th>Baseline colonoscopy: most advanced finding(s)</th>
<th>Recommended surveillance interval (y)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No polyps</td>
<td>10</td>
</tr>
<tr>
<td>Small (&lt;10 mm) hyperplastic polyps in rectum or sigmoid</td>
<td>10</td>
</tr>
<tr>
<td>1–2 small (&lt;10 mm) tubular adenomas</td>
<td>5–10</td>
</tr>
<tr>
<td>3–10 tubular adenomas</td>
<td>3</td>
</tr>
<tr>
<td>&gt;10 adenomas</td>
<td>&lt;3</td>
</tr>
<tr>
<td>One or more tubular adenomas ≥10 mm</td>
<td>3</td>
</tr>
<tr>
<td>One or more villous adenomas</td>
<td>3</td>
</tr>
<tr>
<td>Adenoma with HGD</td>
<td>3</td>
</tr>
</tbody>
</table>

**Serrated lesions**

- Sessile serrated polyp(s) <10 mm with no dysplasia:
  - 5
- Sessile serrated polyp(s) ≥10 mm:
  - 3
- OR
- Sessile serrated polyp with dysplasia:
  - OR
- Traditional serrated adenoma:

**Serrated polyposis syndrome**

- 1
Reviewed 2260 colonoscopies found to have SSAs and/or traditional adenomas
- 788 with subsequent surveillance colonoscopy (mean interval: ~ 4 years)

Assessed rates of subsequent advanced adenoma and SSPs
- SSAs alone
- Low-risk TA alone
- High risk TAs alone
- SSAs in combination with TAs
“low risk” SSP alone

- Significantly higher rate of metachronous advanced adenoma than for non-SSP low-risk adenoma (p=0.019)
- Similar risk to
  - non-SSA high-risk adenomas
  - Low-risk traditional adenomas with low risk SSAs

<table>
<thead>
<tr>
<th></th>
<th>Rate of Subsequent Advanced Adenoma</th>
<th>Rate of Subsequent SSA</th>
</tr>
</thead>
<tbody>
<tr>
<td>LRA + SSP</td>
<td>12/66 (18.2%)</td>
<td>22/66 (33/3%)</td>
</tr>
<tr>
<td>LRA, No SSP</td>
<td>29/370 (7.8%)</td>
<td>16/370 (4.3%)</td>
</tr>
<tr>
<td>Low risk SSP alone</td>
<td>10/56 (17.9%)</td>
<td>n/a</td>
</tr>
<tr>
<td>HRA no SSP</td>
<td>40/252 (15.9%)</td>
<td>15/252 (6.0%)</td>
</tr>
</tbody>
</table>
Case #5: Surveillance of Sessile Serrated Adenoma

- **Question 8:** When would you perform the next surveillance colonoscopy?
  
  A) 1-2 years  
  B) ~ 3 years  
  C) ~ 5 years  
  D) ~ 10 years  

- **Question 9:** What is the risk of finding a metachronous high-risk lesion in the next 5 years
  
  A) 5-10%  
  B) 10-15%  
  C) 15-20%  
  D) >20%
Case #6: Prevention of Post-ERCP Pancreatitis

- 63 y.o female presented with elevated bilirubin, severe RUQ pain
- Abdominal u/s shows
  - CBD dilated to 1.7cm
  - Cholelithiasis
- Otherwise healthy, no prior history of GI or biliary disease
- An ERCP is booked
Case #6: Prevention of Post-ERCP Pancreatitis

Which is the following would you recommend?

A) Rectal indomethacin following ERCP if high-risk patient-related or procedural risk factors

B) Rectal indomethacin prior to ERCP if patient-related risk factors, PLUS following ERCP if procedure related risk factors

C) Rectal indomethacin prior to ERCP in all persons, regardless of risk factors
Case #6: Prevention of Post-ERCP Pancreatitis

- Post ERCP pancreatitis occurs following 5-10% of ERCPs

- Risk Factors include
  - Patient related
    - History of ERCP pancreatitis
    - Multiple episodes of pancreatitis
    - Young females
  - Procedural related
    - Multiple injection of pancreatic ducts
    - Acinarization
    - Pancreatic sphincterotomy
    - Precut sphincterotomy
Post-procedural rectal indomethacin in high risk patients

- Significant reduction in rates of:
  - Any post ERCP pancreatitis (9.2% vs 16.9%, p=0.005)
  - Severe post-ERCP pancreatitis (4.4% vs 8.8%, p=0.03)
Case #6: Prevention of Post-ERCP Pancreatitis

- **Benefits of universal pre-procedural NSAIDs**
  - Don’t always know who will have procedural risk factors before hand
  - May have benefits in low-risk patients as well

- **Drawbacks**
  - Increased costs
  - Risks of gastrointestinal bleeding, renal failure
Physician blinded RCT comparing
- Universal pre-procedure rectal indomethacin
- Selected post-procedure rectal indomethacin in high risk patients
  - 2600 subjects
  - No prior Hx of ERCP pancreatitis
  - ~80% performed for evaluation of CBD stones

Evaluated rates of post-ERCP pancreatitis and complications
<table>
<thead>
<tr>
<th>Event</th>
<th>Pre-procedural indometacin in all patients (n=1297)</th>
<th>Post-procedural indometacin in high-risk patients* (n=1303)</th>
<th>Relative risk (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post-ERCP pancreatitis</td>
<td>47 (4%)</td>
<td>100 (8%)</td>
<td>0.47 (0.34–0.66)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Mild</td>
<td>36 (3%)</td>
<td>77 (6%)</td>
<td>0.47 (0.32–0.69)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Moderate to severe</td>
<td>11 (1%)</td>
<td>23 (2%)</td>
<td>0.48 (0.24–0.98)</td>
<td>0.040</td>
</tr>
<tr>
<td>Post-ERCP pancreatitis in high-risk patients*</td>
<td>18/305 (6%)</td>
<td>35/281 (12%)</td>
<td>0.47 (0.27–0.82)</td>
<td>0.0057</td>
</tr>
<tr>
<td>Mild</td>
<td>14 (5%)</td>
<td>29 (10%)</td>
<td>0.45 (0.24–0.82)</td>
<td>0.0079</td>
</tr>
<tr>
<td>Moderate to severe</td>
<td>4 (1%)</td>
<td>6 (2%)</td>
<td>0.61 (0.18–2.15)</td>
<td>0.44</td>
</tr>
<tr>
<td>Post-ERCP pancreatitis in average-risk patients</td>
<td>29/992 (3%)</td>
<td>65/1022 (6%)</td>
<td>0.46 (0.30–0.71)</td>
<td>0.0003</td>
</tr>
<tr>
<td>Mild</td>
<td>22 (2%)</td>
<td>48 (4%)</td>
<td>0.47 (0.29–0.78)</td>
<td>0.0024</td>
</tr>
<tr>
<td>Moderate to severe</td>
<td>7 (1%)</td>
<td>17 (2%)</td>
<td>0.42 (0.18–1.02)</td>
<td>0.048</td>
</tr>
<tr>
<td>Gastrointestinal bleeding</td>
<td>13 (1%)</td>
<td>10 (1%)</td>
<td>1.31 (0.57–2.97)</td>
<td>0.52</td>
</tr>
<tr>
<td>Mild</td>
<td>5 (&lt;1%)</td>
<td>4 (&lt;1%)</td>
<td>1.26 (0.34–4.67)</td>
<td>0.75</td>
</tr>
<tr>
<td>Moderate</td>
<td>6 (&lt;1%)</td>
<td>5 (&lt;1%)</td>
<td>1.21 (0.37–3.94)</td>
<td>0.78</td>
</tr>
<tr>
<td>Severe</td>
<td>2 (&lt;1%)</td>
<td>1 (&lt;1%)</td>
<td>2.01 (0.18–22.13)</td>
<td>0.62</td>
</tr>
<tr>
<td>Biliary infection</td>
<td>22 (2%)</td>
<td>33 (3%)</td>
<td>0.67 (0.39–1.14)</td>
<td>0.14</td>
</tr>
<tr>
<td>Mild</td>
<td>15 (1%)</td>
<td>24 (2%)</td>
<td>0.63 (0.33–1.19)</td>
<td>0.15</td>
</tr>
<tr>
<td>Moderate</td>
<td>7 (1%)</td>
<td>9 (1%)</td>
<td>0.78 (0.29–2.09)</td>
<td>0.62</td>
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<tr>
<td>Severe</td>
<td>0</td>
<td>0</td>
<td>..</td>
<td>..</td>
</tr>
<tr>
<td>Perforation</td>
<td>1 (&lt;1%)</td>
<td>0</td>
<td>..</td>
<td>..</td>
</tr>
<tr>
<td>Other adverse events</td>
<td>5 (&lt;1%)</td>
<td>5 (&lt;1%)</td>
<td>..</td>
<td>..</td>
</tr>
<tr>
<td>Pulmonary infection</td>
<td>2 (&lt;1%)</td>
<td>5 (&lt;1%)</td>
<td>0.40 (0.08–2.07)</td>
<td>0.45</td>
</tr>
<tr>
<td>Incomplete bowel obstruction</td>
<td>3 (&lt;1%)</td>
<td>0</td>
<td>..</td>
<td>..</td>
</tr>
<tr>
<td>Length of post-ERCP hospital stay (days)</td>
<td>2 (1–4)</td>
<td>3 (1–4)</td>
<td>..</td>
<td>0.17</td>
</tr>
</tbody>
</table>
Case #6: Prevention of Post-ERCP Pancreatitis

Which is the following would you recommend?

A) Rectal indomethacin following ERCP if high-risk patient-related or procedural risk factors

B) Rectal indomethacin prior to ERCP if patient-related risk factors, PLUS following ERCP if procedure related risk factors

C) Rectal indomethacin prior to ERCP in all persons, regardless of risk factors
Case #7: Management of LGD in Barrett’s Esophagus

- 72 y.o male with HTN, DM2, History of GERD

- 5 years ago, EGD showed nondysplastic BE, 3cm circumferential, 5cm maximal length. On chronic PPI

- f/u EGD this year
  - No visible lesions
  - 4 quadrant biopsies every 2cm

- Histology reveals
  - 1 biopsy with LGD, confirmed with second expert pathologist
Case #7: Management of LGD in Barrett’s Esophagus

- Question 11: If a confirmation endoscopy with 4 quadrant biopsies is performed, what is the likelihood of not finding LGD again
  
  A) ~10%
  B) ~25%
  C) ~35%
  D) ~50%

- Question 12: If LGD is found again on a repeat EGD, what is the estimated annual rate of progression to HGD or EAC
  
  A) 1% per year
  B) 3% per year
  C) 5% per year
  D) 8% per year
Review of 1579 cases in a Dutch database demonstrating LGD
  • Confirmed with second pathologist in 161 cases
Barrett's esophagus with low-grade dysplasia

Referral to an endoscopist with expertise in management of dysplasia and capability of performing endoscopic resection

Confirm diagnosis with ≥1 expert GI pathologist

Yes

Repeat upper endoscopy by expert using high-definition white light endoscopy under maximal acid suppression within 8–12 weeks

- Surveillance biopsies (4 quadrant q1–2 cm)
- Endoscopic resection of visible lesions

Expert GI pathology review

High-grade dysplasia/ intramucosal cancer

Endoscopic eradication therapy

Low-grade dysplasia confirmed

Discuss risks and benefits of endoscopic eradication therapy vs. surveillance

Yes

Decision to proceed with endoscopic eradication therapy

Radiofrequency ablation: goal of complete eradication of intestinal metaplasia

Enroll in surveillance program post-endoscopic eradication therapy

- Surveillance EGD every year for 2 years and then every 3 years

No

Diagnosis downgraded to non-dysplastic Barrett's esophagus

Surveillance endoscopy

- Every 3–5 years
- Separate biopsies for visible abnormalities
- 4 quadrant biopsies every 2 cm

Non-dysplastic Barrett's esophagus
Case #7: Management of LGD in Barrett’s Esophagus

- Question 11: If a confirmation endoscopy with 4 quadrant biopsies is performed, what is the likelihood of not finding LGD again
  - A) ~10%
  - B) ~25%
  - C) ~35%
  - D) ~50%

- Question 12: If LGD is found again on a repeat EGD, what is the estimated annual rate of progression to HGD or EAC
  - A) 1% per year
  - B) 3% per year
  - C) 5% per year
  - D) 8% per year
Case #8: Low FODMAP diets for IBS

- 22 y.o female, new consultation for IBS-D
  - Diagnosed by Fam MD
  - Has tried increasing fibre intake and curtailing caffeine with inconsistent effects

- Has heard through friends about low FODMAP diet
Case #8: Low FODMAP diets for IBS

Question 13: Which of the following statement about the use of a low FODMAP diet is not supported by RCT evidence

A) A diet low in FODMAPs is superior to conventional dietary advice in leading to overall reduction in IBD symptoms

B) A low FODMAP diet decreased abdominal pain more than conventional dietary advice

C) A low FODMAP diet decreased bloating more than conventional dietary advice
A Randomized Controlled Trial Comparing the Low FODMAP Diet vs. Modified NICE Guidelines in US Adults with IBS-D

- 92 people in RCT
  - 50 randomized to low FODMAP diet
  - 42 to standard IBS diet, modified as not to advice reduction in FODMAPs
  - 4 week trial

- Primary endpoint
  - Subjective Adequate Relief of IBS symptoms in final 2 weeks of study
  - Also looked at individual rating scores for bloating, abdominal pain, consistency

*Am J Gastroenterol 2016; 111:1824–1832*
A Randomized Controlled Trial Comparing the Low FODMAP Diet vs. Modified NICE Guidelines in US Adults with IBS-D

**Adequate relief**

- m-NICE: 41% (P=0.3055)
- Low FODMAP: 52%

**Composite end point**

- m-NICE: 13% (P=0.1152)
- Low FODMAP: 27%

**Pain responder**

- m-NICE: 23% (P=0.0083)
- Low FODMAP: 51%

**Consistency responder**

- m-NICE: 28%
- Low FODMAP: 42% (P=0.1812)
RCT comparing

- Low FODMAP diet (n=38) vs non-modified IBS diet
- 4 week trial

Main outcome

- Reduction in IBS Symptom Score by 50 points
FODMAP intake among responder to the low FODMAP diet was 40% lower than in non-responders.
Case #8: Low FODMAP diets for IBS

Question 13:
Which of the following statements about the use of a low FODMAP diet is not supported by RCT evidence

A) A diet low in FODMAPs is superior to conventional dietary advice in leading to overall reduction in IBD symptoms

B) A low FODMAP diet decreased abdominal pain more than conventional dietary advice

C) A low FODMAP diet decreased bloating more than conventional dietary advice
Case #5

- 46 yo M with third visit to the ED for food impaction; self resolved twice before
- Family history of esophageal dilations
- Endoscopic disimpaction reveals white plaques, linear furrowing, feline esophagus

Should PPI be the initial Rx?
A) yes
B) no – fluticasone swallowed
C) no – oral corticosteroids
D) no – elemental diet
PPIs decrease large numbers of eosinophils

• 51 subjects (>40 eos) treated with high dose PPI for 8 weeks and endoscopy performed
• 69% experienced clinico-pathological response
• Less likely if food impaction or eosinophil > 70 eos/HFP

E Gomez-Torrijos et al. APT 2016;43:745-6
PPIs have other mechanisms of action

- Abolish acid production

- Decrease eosinophil chemo-attractants and resolve esophageal eosinophilia
  - Ishimura et al AJG 2016

- Treat Eosinophilic Esophagitis?
Should he receive PPI as treatment?

- Yes.....
  - To fulfill diagnostic criteria and rule out GERD/PPIREE
  - It may be a treatment for esophageal eosinophilia

Mar 22, 2016 ... ”Proton-pump inhibitor-responsive esophageal eosinophilia: an entity challenging current diagnostic criteria for eosinophilic esophagitis”

C Guitierrez-Junquera et al. JPGN 2016;62:704-710
A randomised, double-blind trial comparing budesonide formulations and dosages for short-term treatment of eosinophilic oesophagitis

Stephan Miehlke, Petr Hruz, Michael Vieth, Christian Bussmann, Ulrike von Arnim, Monther Bajbouj, Christoph Schlag, Ahmed Madisch, Christiane Fibbe, Henning Wittenburg, Hans Dieter Allescher, Max Reinshagen, Stefan Schubert, Jan Tack, Michaela Müller, Patrick Krummenerl, Joris Arts, Ralph Mueller, Karin Dilger, Roland Greinwald, Alex Straumann
Management of Eosinophilic Esophagitis in 2017

Suspected EoE
PPI x 8 wks, EGD with biopsy

Symptom resolution
Normal histology

>PPI Responsive Esophageal Eosinophilia”
(“EoE” vs GERD vs. ?)

Eosinophilic Esophagitis

>15 Eos/hpf

Persistence of symptoms
Normal histology

“Persistent Symptoms (and abnormal histology)

Adherence
Change diet
Increase topical dose
Change topical steroid
Systemic steroid
Dilation

Persistent symptoms
and normal histology

Dietary therapy

Topical steroid

Change EoE treatments

Other causes

Symptom relief and
normal histology

Maintenance Therapy
Case #6: Global health in Canada

Parents of three healthy pre-schoolers who attend daycare both develop 3 days of non-bloody watery diarrhea a/w fever, but no vomiting. You advise ORT, but parents ask about alternatives . . .

a) Ondansetron
b) Probiotics
c) Racecadotril
d) Lactose restriction
e) Loperamide

Parents don’t have alternative care plans. How can one reduce the risk of acute enteric infections?

a) Hand washing
b) Smectite
c) Oral antibiotics
d) Prebiotics
e) Rotavirus vaccination
Families should be encouraged to have a supply of oral rehydration solution (ORS) at home.
# Level of evidence supporting recommendations

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</tr>
</thead>
<tbody>
<tr>
<td>Dehydration signs</td>
<td>-</td>
<td>+</td>
<td>+</td>
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</table>

Strong evidence classified as “High level” in GRADE system and “I” in Muir–Gray & Cook. Data coming from metanalysis and more than 1 RCT

Moderate evidence classified as “Moderate level” in GRADE system and “II” in Muir–Gray & Cook. Data coming from RCT

Low evidence classified as “Low level” in GRADE system and “III” in Muir–Gray & Cook. Data coming from cohort and observational studies

Poor evidence classified as “Very low level” in GRADE system and “IV or V” in Muir–Gray & cook. Data coming from case series, case report and expert opinion

No reference supporting the guidelines’ recommendations or level of evidence not reported

Recommendation not reported in the guidelines
Emerging therapies for acute diarrhea

Racecadotril (acetorphan):
• Thiorphan is the active metabolite
• Encephalinase inhibitor
• Acts as an anti-secretory agent
• Licensed in many countries, but not USA
• 3 RCT’s of 1.5 mg/kg po tid
642 subjects, 540 >1 mo & <6 yr age
diarrhea -53.5 hr (95% CI: -65.6, -41.3)

M Piescik-Lech et al. APT 2013;37:289-303
Other novel therapies for acute diarrhea

Serotonin-3 receptor antagonists (in IBS-D)
ramosetron

*S Fukudo et al. Gastroenterology 2016;150:358-66*

Na+/HCO3- co-transporter target (in enteroids)

*J Foulke-Abel et al. Gastroenterology 2016;150:638-49*

Smectite (diosmectite): absorbent clay

Relative effectiveness analysis of ORT adjuncts

Systematic review and network meta-analysis underway . . .

*ID Florez et al. Systematic Reviews 2016;5:14*
RCT of hand-washing with soap and chlorine treatment of water
Dhaka, Bangladesh

47% reduction in *Vibrio cholerae* infections!


Rotavirus vaccine impacts health:

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>No. of hospitalizations</td>
<td>110,688</td>
<td>73,778</td>
<td>82,703</td>
<td>36,890</td>
<td>27,965</td>
<td>64,855</td>
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<td>Cost of hospitalizations ($)</td>
<td>473,770,195</td>
<td>315,842,541</td>
<td>354,051,300</td>
<td>157,927,653</td>
<td>119,718,894</td>
<td>277,646,547</td>
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</table>

USA: JE Cortes et al. NEJM 2011;365:1108-117

Case #7

35 yo F with jaundice and pruritus
PEx: hepatomegaly
• no stigmata of chronic liver disease
Laboratory:
• increased LET’s
• elevated conjugated bilirubin
• normal LFT’s
No response to empiric trial of UDCA

Next steps?:
A) IgG4 level
B) Colonoscopy
C) MRCP
D) Liver biopsy
Any new therapies to consider . . .
A Placebo-Controlled Trial of Obeticholic Acid in Primary Biliary Cholangitis


2016;375:631-643

Phase 3, 12-month RCT
Farsenoid X receptor agonist
US 70,000. per year
Delivered Significant, Sustained Reductions in Alkaline Phosphatase

**Mean Alkaline Phosphatase Over 12 Months**

- Placebo + UDCA (n=73)
- OCALIVA 5→10 mg Titration + UDCA (n=70)
- OCALIVA 10 mg + UDCA (n=73)

*In the trial there were 16 patients (7%) who were intolerant and did not receive concomitant UDCA: 6 patients (8%) in the OCALIVA 10 mg arm, 5 patients (7%) in the OCALIVA titration arm, and 5 patients (7%) in the placebo arm.

ALP, alkaline phosphatase; UDCA, ursodeoxycholic acid; ULN, upper limit of normal.
Case #8

35 yo M with sleep apnea
PEx: hypertensive
BMI 45

Laboratory:
- elevated AST, ALT
- normal bilirubin
- normal LFT’s
- raised TG and cholesterol
- hepatomegaly on AUS elastography normal
- MRE normal

What therapies should one offer?:

A) Non-pharmacological
B) Surgical intervention
C) Antioxidant cocktail
D) GLP-1 analogue
Multiple hit hypothesis
• Glucose-induced GLP-1 secretion is diminished in adults with NAFLD
• Liraglutide is a long acting GLP-1 analogue licensed for the treatment of type 2 diabetes

Liraglutide safety and efficacy in patients with non-alcoholic steatohepatitis (LEAN): a multicentre, double-blind, randomised, placebo-controlled phase 2 study


- Phase 2, double-blinded, RCT
  - 4 medical centers in UK
- Overweight patients with NASH
- SQ liraglutide (1.8 mg daily) x 48 weeks
  - vs. placebo; n=26 in each group
- Primary outcome: resolution of definite NASH without fibrosis progression
Liraglutide safety and efficacy in patients with non-alcoholic steatohepatitis (LEAN): a multicentre, double-blind, randomised, placebo-controlled phase 2 study


Lancet 2016:387:679-690

Weight: 

![Graph A](#)  

HbA1c

![Graph B](#)  

AST:

![Graph C](#)  

GGTP

![Graph D](#)
Case #9: Prevention of Recurrent ASA-Related UGI Bleeding

- 77 y.o male with past Hx of MI, HTN, on ASA 81mg/d
- Presented 8 weeks ago with UGIB, endoscopy revealed multiple gastric erosions
- HP –ve on biopsy and serology
- Treated with PPI for past 8 weeks
- Today, expressed concern about recent news linking PPI use to dementia
Case #9: Prevention of Recurrent ASA-Related UGI Bleeding

Question 14:

- Would you consider using an H2RA to prevent recurrent upper gastrointestinal bleeding

A) Insist on PPI Therapy

B) Consider Use of H2RAs if PPIs will not be used

C) Discontinue ASA therapy, as risk of recurrent bleeding is too great if PPIs not used
Case #9: Prevention of Recurrent ASA-Related UGI Bleeding

- ACCF/AHA/ACG 2008 consensus recommends PPIs as gastroprotection for persons using ASA at high risk of UGIB
  - History of PUD/UGIB
  - Age > 65
  - Use of multiple anti-platelets/anticoagulants
  - Severe medical comorbidity
  - Systemic corticosteroid use

- Increased concerns about PPIs and serious medical complications
  - CDAD
  - Hip fracture
  - Dementia
  - CVA
  - Pneumonia

- No proven direct causal relationship, but clinicians and patients are jittery
Compared ESO 20 bid to Famotidine 20mg bid, n=130

Trend towards lower rates of UGIB with PPI vs H2RA
- 0% vs. 7.5%
  - P=0.058
RCT of 270 people randomized with endoscopically confirmed PUD bleeding
- On ASA < 325mg/d
- HP –ve

Randomized to
- Rabeprazole 20mg/d
- Famotidine 40mg/d

Followed every 2 months for symptoms up to 12 months

Endoscopy repeated for UGI symptoms or evidence of recurrent UGIB
Rate of recurrent UGIB
PPI: 0.7% (0.1 - 5.1%)
H2RA: 3.1% (1.2 - 8.1%)
Case #9: Prevention of Recurrent ASA-Related UGI Bleeding

Question 14:
- Would you consider using an H2RA to prevent recurrent upper gastrointestinal bleeding

A) Insist on PPI Therapy

B) Consider Use of H2RAs if PPIs will not be used

C) Discontinue ASA therapy, as risk of recurrent bleeding is too great if PPIs not used
Case #10: Management of Achalasia

- 67 y.o male with 5 year history of progressive dysphagia
  - First to solids, now to all foods

- Diagnosed with Type 1 Achalasia on the basis of esophageal manometry

- Wants definitive therapy
Case #10: Management of Achalasia

Question 15:

- According to a recent RCT, which is the preferred strategy for definitive management of achalasia?

A) Laparoscopic Heller Myotomy (LHM)
B) Pneumatic Dialation (PD)
C) No difference between LHM and PD
RCT comparing PD and LHM
- 105 in LHM, 98 to PD

In PD arm,
- Allowed to have 2 redilations in first 24 months, one additional in 60 months
- 2 analysis
  - Redilations allowed
  - Redilations considered as treatment failure
In subgroup analysis

- Type 1: LHM 75%, PD 69%
- Type 2: LHM 88%, PD 96% (p=0.03)
- Type 3: LHM 86%, PD 44% (p=0.10)

Younger age, chest pain and esophageal dilation > 4cm associated with treatment failure
Case #10: Management of Achalasia

Question 15: According to a recent RCT, which is the preferred strategy for definitive management of achalasia?

A) Laparoscopic Heller Myotomy (LHM)
B) Pneumatic Dialation (PD)
C) No difference between LHM and PD
Liraglutide safety and efficacy in patients with non-alcoholic steatohepatitis (LEAN): a multicentre, double-blind, randomised, placebo-controlled phase 2 study


Lancet 2016:387:679-690
Case #9

25-year-old F with 3 year history of IBS-diarrhea predominant (Rome IV) that began after an acute episode of bloody diarrhea affecting the entire family.

What intervention has a NNT of just 7?

a) Cognitive behavioral therapy
b) Probiotics
c) Low Fermentable Oligosaccharides, Disaccharides, Monosaccharides and Polyols (FODMAPs) diet
d) Tricyclic antidepressants
e) SSRIs
Rome IV

Functional Gastrointestinal Disorders:
Disorders of Gut-Brain Interaction
Microbiome-gut-brain communication

A Complicated Conversation

The interplay between the digestive tract and the central nervous system is well-established. Signals produced by the gut microbiota are thought to influence this gut-brain axis. If they do, disruptions to this community of bacteria could have a role in exacerbating symptoms of irritable bowel syndrome.

The microbiota is thought to influence mood and cognition, possibly by signalling to the brain through the vagus nerve or stimulating production of neurotransmitters in the gut. But this has been shown only in animal studies.

The brain regulates digestive-tract activity. The gut communicates with the brain through the vagus nerve.

Effects of environmental stress on the brain can have a lasting impact on gut health.

Disrupted gut function can change the microbiota’s composition or metabolic activity.

Pathogenic bacteria or overexposure to antibiotics may kill off microbes that assist gut function.

Supplementation with ‘good’ bacteria, or probiotics, may restore the microbiota.


Nature 2016;533:S104-S106
How does one increase diversity?

- Lactate producers (e.g., lactobacilli, bifidobacteria)
- Methanogens (e.g., methanogenic archaea)
- Mucin degraders (e.g., Bacteroidetes)
- Short chain fatty acids producers (e.g., Clostridium)

Fecal transplant (100s of strains, undefined composition)

Consortium (defined composition of more than one strain, which together, perform a function of interest)

Single strain (one strain, pure isolate)

Bioactive (molecule produced by strain that mediates effect on host)


“Precision microbiome reconstitution”

C Buffie et al. Nature 2015;517:205-208
Probiotics reduce symptoms of functional abdominal pain in childhood

S Guandalini et al. JPGN 2010;51:24-30 (VSL#3)
A Gawronska et al. APT 2007;25:177-184 (LGG)
Probiotics vs. placebo in adults with IBS

NNT = 7

# Comparison of Profiles of *L. plantarum* and *B. infantis*

<table>
<thead>
<tr>
<th>Bacterial Strain</th>
<th>Product Name</th>
<th>IBS Indication Approved by Health Canada</th>
<th>Allergen Safety</th>
<th>Dose and Cost</th>
<th>Storage</th>
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<tbody>
<tr>
<td><em>Lactobacillus plantarum</em> 299v</td>
<td>TuZen</td>
<td>Helps to reduce flatulence and abdominal pain associated with flatulence in individuals with IBS</td>
<td>No lactose or milk protein but has contact with soy</td>
<td>1 cap bid x1wk and then 1/day for maintenance Cost: 30 capsules: $36.99* Average Monthly Maintenance Cost: $36.99/ month (as of May, 2011)*</td>
<td>Room temperature in a dry place (hot months may need to refrigerate) until labelled expiry date</td>
</tr>
<tr>
<td><em>Bifidobacterium longum</em> subsp. <em>infantis</em> 35624 (Bifantis™)</td>
<td>Align</td>
<td>For relief and management of IBS symptoms. Relieves symptoms of Irritable Bowel Syndrome (IBS) such as abdominal discomfort, gas, and bloating. With daily use, provides ongoing relief of IBS symptoms such as abdominal discomfort, gas, and bloating.</td>
<td>No lactose or soy but there is milk protein in the ingredients</td>
<td>1 cap once daily Cost: 28 capsules: $36.00* Average Monthly Maintenance Cost: $38.57/ month (as of May, 2011)*</td>
<td>Room temperature until labelled expiry date. Recommended to keep in original blister packaging for best shelf life</td>
</tr>
</tbody>
</table>

* Based on an average retail cost range of $32–40 per package and a 30-day month.
Case #10

90 yo F in nursing home with repeated bouts of diarrhea, incontinence, quality of life: nil

PEx: withdrawn, sarcopenic, BMI 15

Laboratory:
Hypokalemia
Hypocalcemia, but free ionized Ca normal
Low alkaline phosphatase, and low zinc

*C. difficile* toxin + on 5 separate tests

What therapies could be considered?:

a) Antibiotics (combination, repeated, newish)

b) Monoclonal antibodies

c) Probiotics

d) Zinc

e) FMT (what if she has a history of IBD?)

[Image: http://www.gettyimages.ca/detail/photo/clostridium-difficile-bacteria-coloured]
Effect of Fecal Microbiota Transplantation on Recurrence in Multiply Recurrent *Clostridium difficile* Infection

A Randomized Trial

Colleen R. Kelly, MD; Alexander Khoruts, MD; Christopher Staley, PhD; Michael J. Sadowsky, PhD; Mortadha Abd, MD; Mustafa Alani, MD; Brianna Bakow, BA; Patrizia Curran, MD; Joyce McKenney, MS; Allison Tisch, NP; Steven E. Reinert, MS; Jason T. Machan, PhD; and Lawrence J. Brandt, MD

![Graph showing the effect of FMT on recurrence in multiply recurrent *Clostridium difficile* infection.](image)
Fecal Microbiota Transplantation Induces Remission in Patients With Active Ulcerative Colitis in a Randomized Controlled Trial

Paul Moayyedi,¹ Michael G. Surette,¹ Peter T. Kim,²,³ Josie Libertucci,¹ Melanie Wolfe,¹ Catherine Onischi,³ David Armstrong,¹ John K. Marshall,¹ Zain Kassam,⁴ Walter Reinisch,¹ and Christine H. Lee³

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

Noortje G. Rossen,¹ Susana Fuentes,² Mirjam J. van der Spek,¹ Jan G. Tijssen,³ Jorn H. A. Hartman,² Ann Duflo,¹ Mark Löwenberg,¹ Gijs R. van den Brink,¹ Elisabeth M. H. Mathus-Vliegen,¹ Willem M. de Vos,²,⁴ Erwin G. Zoetendal,² Geert R. D’Haens,¹ and Cyriel Y. Ponsioen¹

177 VEGFR2 Signaling Inhibits Senescence and Promotes Colorectal Cancer

ALSO:
- RESEARCH PRIORITIES FOR ALCOHOLIC HEPATITIS 4
- REVIEW: AUTOIMMUNE PANCREATITIS 39
Meta-analysis of RCTs of FMT in UC: remission rates

- 3 RCTs, 204 patients
- NNT = 6 (95% CI = 4 to 14)
- RR = 0.81 (95% CI = 0.71-0.92), p=0.001
- I² = 0%
- GRADE = moderate quality evidence

Slide courtesy of P. Moayyedi, CCC Future Directions in IBD
Toronto, November, 2016
Case #11

17.5 yo M with autism spectrum disorder, and
• generalized irritability (possible pain)
• chronic constipation
• abdominal bloating

PEx:
• BMI 35
• developmental delay

Laboratory:
• elevated acute phase reactants
• normal fecal calprotectin
• colonic impaction on AXR
• peptic esophagitis on 3 upper endoscopies
• nodular lymphoid hyperplasia at ileoscopy

How (well) are you going to handle taking over his long-term care?
Risks in Transitions in Care

- Information Accuracy
- Information Sharing
- Information Continuity

Discontinuous
Poor Coordination
Poor Quality
Compromised Patient Safety
Unfavourable Experiences

Slide courtesy of: Dr. Brian Rowe, Univ. Alberta
Transitions in Pediatric Gastroenterology: Results of a National Provider Survey


<table>
<thead>
<tr>
<th>Aspect of transition care</th>
<th>Pediatric GI providers, N = 150 mean (±SD)</th>
<th>Adult GI providers, N = 363 mean (±SD)</th>
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<tbody>
<tr>
<td>Knowledge of name, dose, and major adverse effects of medication (medical condition)</td>
<td>4.4 ± 0.6</td>
<td>4.6 ± 0.6</td>
</tr>
<tr>
<td>Knowledge of own medical history (medical condition)</td>
<td>4.4 ± 0.6</td>
<td>4.5 ± 0.6</td>
</tr>
<tr>
<td>Conception of disease and its basic nature (medical condition)</td>
<td>4.7 ± 0.5</td>
<td>4.7 ± 0.5</td>
</tr>
<tr>
<td>Filling prescriptions (medical condition)</td>
<td>4.5 ± 0.6</td>
<td>4.3 ± 0.9</td>
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<tr>
<td>Active participation during office visits (independence)</td>
<td>4.5 ± 0.6</td>
<td>4.4 ± 0.7</td>
</tr>
<tr>
<td>Attending office visits alone (independence)</td>
<td>4.0 ± 0.7</td>
<td>3.2 ± 1.1</td>
</tr>
<tr>
<td>Identification of people involved in their health care (both family and professionals) (medical condition)</td>
<td>4.3 ± 0.6</td>
<td>4.4 ± 0.7</td>
</tr>
<tr>
<td>Initiate contact (by telephone or e-mail) if a problem arises between visits (independence)</td>
<td>4.4 ± 0.6</td>
<td>4.3 ± 0.9</td>
</tr>
</tbody>
</table>

GI = gastrointestinal. Responses provided on a Likert scale from 1 to 5, in which 1 represented “not important at all” and 5 represented “very important.”

*Responses from adult gastroenterology providers taken from Hait et al (13).
Bridging the cultures of pediatric and adult medicine:

**Pediatric Health Care providers:**
- may be reluctant to transfer care
- may communicate anxiety to parents/families
- used to allied health support resources
- don’t always transfer requisite information

**Internal Medicine Health Care practitioners:**
- may want to reassess (“baseline”)
- may want to change management
- change timing of interval follow-ups
- more limited access to allied health care
- parental involvement adds another dimension
<table>
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<tr>
<th>Barriers</th>
<th>Percentage</th>
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<td>Parent’s/guardian’s attachment to pediatric health care providers</td>
<td>81</td>
</tr>
<tr>
<td>Patient’s attachment to pediatric health care providers</td>
<td>74</td>
</tr>
<tr>
<td>Patient emotional/cognitive delay</td>
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### Rapid-fire 2016 papers for CDDW-2017

#### ANSWERS to Questions

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