ACP 2016
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Colorectal cancer (CRC)
- Update on screening strategies and tools

Irritable Bowel Syndrome (IBS)
- New therapeutic options

C-difficile
- Updates on treating recurrent disease
CRC Facts

- Third most common cancer diagnosis
- 5% lifetime risk
- 95,270 new cases of colon cancer in 2016

Cancer.org
JAMA 2016.
CRC Facts

* Second most common cause of cancer death
* 49,190 deaths related in 2016

Silver Lining:
* Death rate has dropped over past decade
  * Improved screening
  * Better treatment

Cancer.org
NEJM 2013
Screening Prevalence

The map illustrates the screening prevalence across the United States. States are color-coded to indicate different prevalence ranges:

- Light green: 57.1 - 61.4
- Medium green: 61.5 - 65.8
- Dark green: 65.9 - 70.4
- Very dark green: 70.5 - 75.6

States with the highest screening prevalence are shown in very dark green. This visualization helps in understanding the distribution and magnitude of screening programs across various states.
CRC Screening

- Prospective cohort study
- 88,902 over 22 years
- Results:
  - Endoscopy vs. No endoscopy
  - Reduced incidence/mortality of distal and proximal cancers
- Large meta-analysis
  - Significant reduction in incidence/mortality

NEJM 2013.
AJG 2016.
CRC Facts

* Risk Factors:
  * Family history
  * Age
  * Gender
  * Ethnicity
  * IBD
  * Diabetes
  * Lifestyle
    * Red meat
    * Alcohol
    * Processed meat
    * Smoking

* Protective
  * Physical activity
  * Dairy consumption
  * Fruit consumption
  * Vegetable consumption
  * High fiber - >10 grams/d
CRC Screening

* Screening options:
  * Cancer prevention tests
    * Colonoscopy and Sigmoidoscopy
  * Cancer detection tests
    * CT colonography
    * Barium Enema
    * FIT testing
    * Cologuard
    * Serum testing
CRC Screening

- Stool based tests:
  - gFOBT
    - Up to 79% sensitivity reported
    - Need 3 samples collected at home
    - Easy and noninvasive
  - FIT
    - Improved sensitivity in some studies
    - Less dietary/medication modifications
    - Optimal number of samples not known

CRC Screening

- Stool DNA – Cologuard
  - Recently added to guidelines for screening
  - Detects DNA biomarkers shed into stool
    - KRAS mutations, aberrant NDRG4/BMP3 methylation
  - Combines with FIT to detect blood
  - Screening: annual (USPSTF), q3 years (manufacturer)
  - Intended for average risk individuals
**CRC Screening**

- **Stool DNA**
  - Compared to FIT (9989 participants)
  - CRC - Sensitivity 92.3% (sDNA) vs. 73.8% (FIT)
  - Advanced adenoma – 42.4 % vs. 23.8%
  - High grade dysplasia and sessile serrated adenomas – outperformed FIT
  - More false positives compared to FIT
- Neg Predictive value
  - 99.94% for Cancer
  - 94.79% for advanced adenoma

NEJM 2014.
CRC Screening

- Serum test
  - SEPT9 assay
  - Improved sensitivity in second generation assay
  - Sensitivity/specificity for CRC – 74.8%/87.4%
    - This increases with stage – Stage IV – 100%
  - Promising results for screening

J Gastroenterology Hepatology 2015.
CRC Screening

- Goal: Get people screened
- Many options available
- Consider the discussion detection vs. prevention tests
- Screening does make a difference
<table>
<thead>
<tr>
<th>Screening Method</th>
<th>Frequency</th>
<th>Evidence of Efficacy</th>
<th>Other Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stool-Based Tests</strong></td>
<td></td>
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<tr>
<td>gFOBT</td>
<td>Every year</td>
<td>RCTs with mortality end points: High-sensitivity versions (eg, Hemoccult SENSA) have superior test performance characteristics than older tests (eg, Hemoccult II)</td>
<td>Does not require bowel preparation, anesthesia, or transportation to and from the screening examination (test is performed at home)</td>
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<tr>
<td>FIT</td>
<td>Every year</td>
<td></td>
<td>Does not require bowel preparation, anesthesia, or transportation to and from the screening examination (test is performed at home)</td>
</tr>
<tr>
<td>FIT-DNA</td>
<td>Every 1 or 3 y</td>
<td></td>
<td>There is insufficient evidence about appropriate longitudinal follow-up of abnormal findings after a negative diagnostic colonoscopy; may potentially lead to overly intensive surveillance due to provider and patient concerns over the genetic component of the test</td>
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<tr>
<td><strong>Direct Visualization Tests</strong></td>
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<tr>
<td>Colonoscopy</td>
<td>Every 10 y</td>
<td>Test characteristic studies</td>
<td>Requires less frequent screening Screening and diagnostic follow-up of positive findings can be performed during the same examination</td>
</tr>
<tr>
<td>CT colonography</td>
<td>Every 5 y</td>
<td></td>
<td>There is insufficient evidence about the potential harms of associated extracolonic findings, which are common</td>
</tr>
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<td>Flexible sigmoidoscopy</td>
<td>Every 5 y</td>
<td>RCTs with mortality end points: Modeling suggests it provides less benefit than when combined with FIT or compared with other strategies</td>
<td>Test availability has declined in the United States</td>
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<tr>
<td>Flexible sigmoidoscopy with FIT</td>
<td>Every 10 y plus FIT every year</td>
<td>RCT with mortality end point (subgroup analysis)</td>
<td>Test availability has declined in the United States Potentially attractive option for patients who want endoscopic screening but want to limit exposure to colonoscopy</td>
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</table>
Irritable Bowel Syndrome (IBS)

- Colic
- Abdominal discomfort
- Stomach bloating
- Altered bowel habit - constipation/diarrhoea
IBS

* Common problem
* Reported to occur up to 28% of population
* Impact on quality of life
* Impact financially
  * Days off work
  * Use of health resources

Gastro 2014.
**IBS**

- Abdominal pain with altered defecation

- **Rome III:**
  - Abd pain/discomfort 3 days/month in last 3 months with 2 of following:
    - Improvement with defecation
    - Associated change in frequency of stooling
    - Associated with change in form of stool
IBS

New therapeutic options:

- Linaclotide (Linzess)
- Rifaximin (Xifaxan)
- Eluxadoline (Viberzi)
- FODMAP diet
IBS

- Linaclotide (Linzess)
  - Activates guanylate cyclase C
    - Activation of CFTR
    - Bicarbonate and Chloride secretion
    - Acceleration of colonic transit and fluid
    - Inhibition of colonic nociceptors – reduction in pain
  - Minimally absorbed
  - Main side effect was diarrhea

Linaclotide (Linzess)
- FDA approved - 2012
  - IBS-C
  - Chronic idiopathic constipation
- Dosing – 290 mcg or 145 mcg daily
- Typically dosed 30min prior to first meal
**IBS**

- Linaclotide (Linzess)
  - 3 RCT compared Linzess to Placebo
    - All met ROME criteria
    - All had constipation and at least 3/10 abd pain
    - Linzess outperformed Placebo
    - Less failure rates for pain and spontaneous BM
      - Pain may take up to 12 weeks to respond
    - Overall improved QL
    - Higher rates of diarrhea

AJG 2012.
Gastro 2010.
**IBS**

- **Rifaximin (Xifaxan)**
  - Evidence that microflora may play role in IBS
  - Broad spectrum
  - Minimal systemic absorption
  - Targets the gut
  - Low risk of bacterial resistance
  - Well tolerated
Rifaximin (Xifaxan)

- FDA approved:
  - IBS-D - 2015
  - Travelers diarrhea
  - Hepatic encephalopathy

- Dose for IBS
  - 550mg TID for 2 weeks

- Expensive
IBS

- Rifaximin (Xifaxan)
  - TARGET 1 & 2 Trial
  - Double blinded, placebo controlled
  - ROME criteria for IBS without constipation
  - Xifaxan 550mg TID for 2 weeks
  - Followed for 10 weeks
  - Symptom response was self reported

Pimental NEJM 2011.
Percentage of Patients with Adequate Relief of Global IBS Symptoms in the TARGET 1 and TARGET 2 Studies Combined.
Rifaximin (Xifaxan)
- Global relief – 40% vs. 31%
- Bloating – 35% vs. 28%
- Abd pain and stool consistency – 44% vs. 36%
- Adverse events were similar
- *TARGET 3
  - Safe and effective to retreat with symptom recurrence

Pimental NEJM 2011.
Gastro 2015.
Eluxadoline (Viberzi)
- FDA approved May 2015
- Approved for IBS-D
- Dosing 75mg or 100mg BID
  - 75 mg dose for cholecystectomy
  - Abdominal pain reported
IBS

* Eluxadoline (Viberzi)
  * Mu Opioid agonist
  * Delta Opioid antagonist
  * Improves diarrhea and abdominal pain
IBS

- Eluxadoline (Viberzi)
  - Clinical response 13.8% vs. 5.7%
  - Improved symptoms:
    - Frequency
    - Urgency
    - Quality of life
  - Adverse effects
    - Abdominal pain
    - Constipation
    - Nausea

Gastro 2013.
IBS

* Lifestyle
  * Smoking cessation
  * Regular physical activity
  * Regular meals
    * Improves symptoms
    * Emotional improvement
    * Improved sleep

**IBS**

- FODMAP diet

- Fermentable Oligosaccharides, Disaccharides, Monosaccharides And Polyols
  - Poorly absorbed short chain carbohydrates
  - Luminal distention b/c osmotic effects
  - Rapid fermentation

Gastro 2014.
IBS

* FODMAP diet
  * Restricting FODMAPS
    * Improved GI symptoms overall
    * Improved – bloating, pain, flatulence
    * Improved stool consistence
    * Long-term tolerability/adherence of concern

Gastro 2014.
Clostridium difficile

- Changing epidemiology
- NAP 1 strain
- Rising resistance
- Difficulty in treating recurrent disease
Rising incidence

- Incidence rates rose by 23% per year from 2000-2005
- 1990’s: 30-40 cases per 100,000
- 2005: 84 per 100,000
- Incidence nearly doubled in all age groups, predominantly effecting the elderly

Increasing severity (mortality rate, longer hospital stays, complications, treatment failures)

- New at risk populations:
  - Younger healthier populations
    - Not previously exposed to Abx
    - Not exposed to hospital or health care environment
  - Young women in the peripartum period

Emerging strain – NAP-1/027

- Initially isolated in the 1984
- This strain is being isolated more frequently
- Factors implicated in outbreaks:
  - Increase production of Toxin A and B
  - Deletion mutation of TcdC protein
  - *A/B 16% and 23% higher
  - Fluoroquinolone resistance
    - **82% resistance in Quebec outbreak
  - Production of binary toxin
    - Thought to act synergistically with toxin A/B

Resistance

- Prior to 2000, failure rates for Vancomycin and Metronidazole were nearly identical (3.5% vs. 2.5%)

- Increasing resistance reported with Metronidazole

- Failure rates up to 26%


Recurrence

- Recurrence rates range from 15-30%
- Rates similar between vancomycin and metronidazole

- Relapse – persistence of the same strain
  - Symptoms occur about 14 days after treatment of initial infection

- Reinfection – acquire a new strain
  - Reportedly 33-75% of cases
  - Symptoms usually occur around 40 days after treatment of previous infection

Recurrence

Risk Factors:

- Previous episode – 40% risk after 1st recurrence to 60% after 2 or more recurrences
- Inadequate antitoxin antibody response
- Persistent disruption of colonic flora
- Advanced age - >65
- Continued use of non-C. difficile antibiotics
- Long hospital stays
- Continued use of antacid medications

*Increase severity of repeat episodes

Treatment

- First recurrence – repeat treatment with same antibiotic
  - If mild symptoms, can follow clinically without antibiotic therapy
- Second Recurrence – A change is warranted
  - 6 week Vancomycin pulse-tapered dosing
- Third or subsequent recurrence
  - Vancomycin pulse-tapered dosing followed by additional strategies
  - Consider FMT

<table>
<thead>
<tr>
<th>Recurrence Level</th>
<th>Treatment Options</th>
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</table>
| Initial recurrence | - 14-day course of oral metronidazole or vancomycin  
|                   | - Consider probiotics |
| Second Recurrence | - Tapered pulse dose oral vancomycin  
|                   |   - 125 mg 4 times daily for 1 week  
|                   |   - 125 mg twice daily for 1 week  
|                   |   - 125 mg daily for 1 week  
|                   |   - 125 mg every other day for 1 week  
|                   |   - 125 mg every third day for 2 weeks  
|                   | - Consider 1-month course of probiotics starting in the final 2 weeks of antibiotic therapy |
| Third or subsequent recurrence | - Tapered pulse dose oral vancomycin (see above)  
| Followed by | - 14-day course of rifaximin, nitazoxanide, or toxin-binding resins  
|           | - Consider 1-month course of probiotics starting in the final 2 weeks of antibiotic therapy  
|           | - Consider intravenous immunoglobulin or fecal bacteriotherapy  
|           | - Consider chronic low-dose suppressive therapy with oral vancomycin for elderly patients and those with multiple comorbidities |
Additional Strategies

- EnteraGam – serum-derived bovine immune globulin
  - Considered a medical food product
  - Requires prescription
  - Used for diarrhea illnesses (HIV, IBS)
  - Thought to bind c-diff toxin A/B
  - Improves gut barrier function/permeability

Investigational Agents:

- Human Monoclonal Antibodies (CDA1, CDB1)
  - Prospective, randomized, double blind, placebo controlled-trial of 200 patients (Phase 2 trial)
  - Both monoclonal antibodies infused together in individuals receiving vanomycin or metronidazole for symptomatic C-diff
  - Primary outcome with recurrence
  - Recurrence 7% Ab, 38% placebo

*Bezlotoxumab

Lowy, I et al. Treatment with Monoclonal Antibodies against Clostridium difficile toxins. NEJM. 2010; 360:197-205.
**Treatment**

- Investigational agents
  - Various Vaccines currently under study
    - ACAM-CDIFF – phase I volunteer safety and immune response, phase II CDI, phase II CDI prevention
    - Intercell IC84 – phase I volunteer safety and immune response
    - Clostridium difficile vaccine – phase I volunteer safety and immune response
Treatment

- Fecal Microbiota Transplantation (FMT)
  - Installation of normal stool
  - Methods:
    - NGT
    - EGD
    - Colonoscopy
    - Enema

- Rationale: imbalance of intestinal microbiota (dysbiosis) produces disease
  - Re-establish an equilibrium

Brandt. ACG.
Treatment

* FMT
  * Early evidence in 4th century China
    * Oral suspension
    * Food poisoning
  * First reported in US 1958
    * Fecal enemas
    * Severe pseudomembranous colitis
  * Cumulative cure around 91%
Treatment

* FMT

* Retrospective review of 18 pt. received stool transplant for recurrent C-diff

15/18 were disease free at 90 days

** Retrospective review of 12 patients who received stool transplant for recurrent c-diff

12/12 had “durable” clinical response

- Symptom free at 3-5 days
- Followed from 3 weeks to 8 years

Treatment

- FMT
  - Good initial and sustained response to FMT
    - 91% at 3 months
    - 86% at 6 months
    - 80% at 18 months
    - Most recurrence related to repeat abx use
  - Effective in critically ill
    - 17 patients with severe colitis – considered for colectomy
    - 88% response rate – avoided colectomy
    - 15/17 symptom free at 3 months

ACG 2014
Treatment

* FMT

* RCT – evaluated FMT nasoduodenal route
  * 16 patients
  * Stopped early
  * 93% response with FMT
  * 30% vancomycin alone
* 97% would repeat FMT
* 58% would choose FMT as primary trx
* No major AE reported

Van Nood et al. NEJM 2013.
Brandt et al. AJG 2012.
FMT

Current practice

- Family donor
- Tested for various infections prior to donation
- Stool collected and mixed with saline
- Roughly 300mL slurry
- Instilled in TI, cecum, ascending, transverse, descending
Treatment

- FMT
  - Pill form is likely next generation FMT
    - Recent study in JAMA
      - 20 patients with recurrent c-diff
      - Cure rate was 90%
      - No major adverse events
  - Frozen specimens
  - Universal donors

Conclusions

- CRC
  - Screening is the goal

- IBS
  - New therapeutics

- C-diff
  - Changing landscape
  - FMT
Questions?