ACP 2016

Aaron Fieker, D.O

- 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
* 39,220 new cases of rectal cancer in 2016

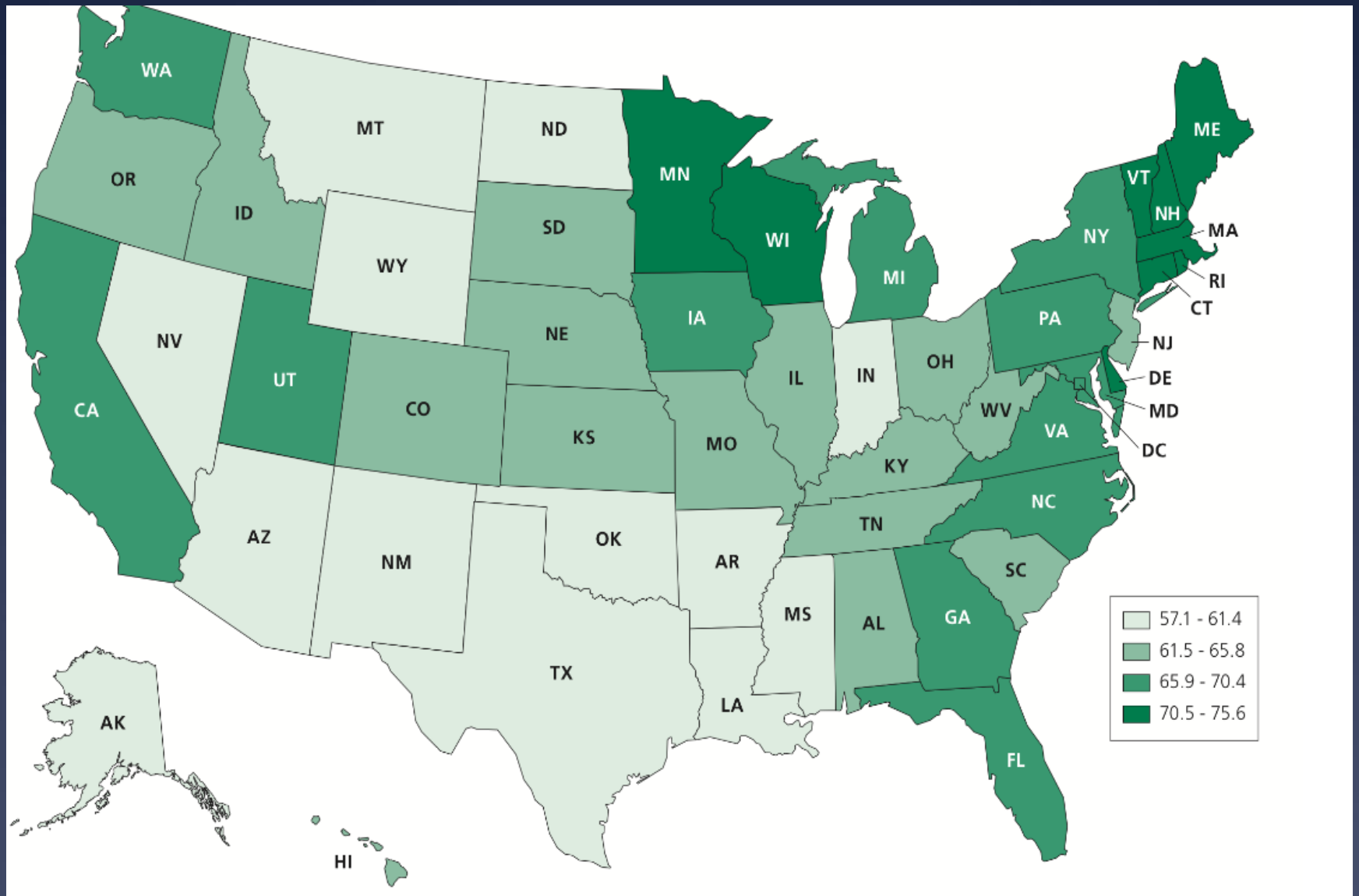
Cancer.org
JAMA 2016.

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



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

CA Cancer J Clin 2008.

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

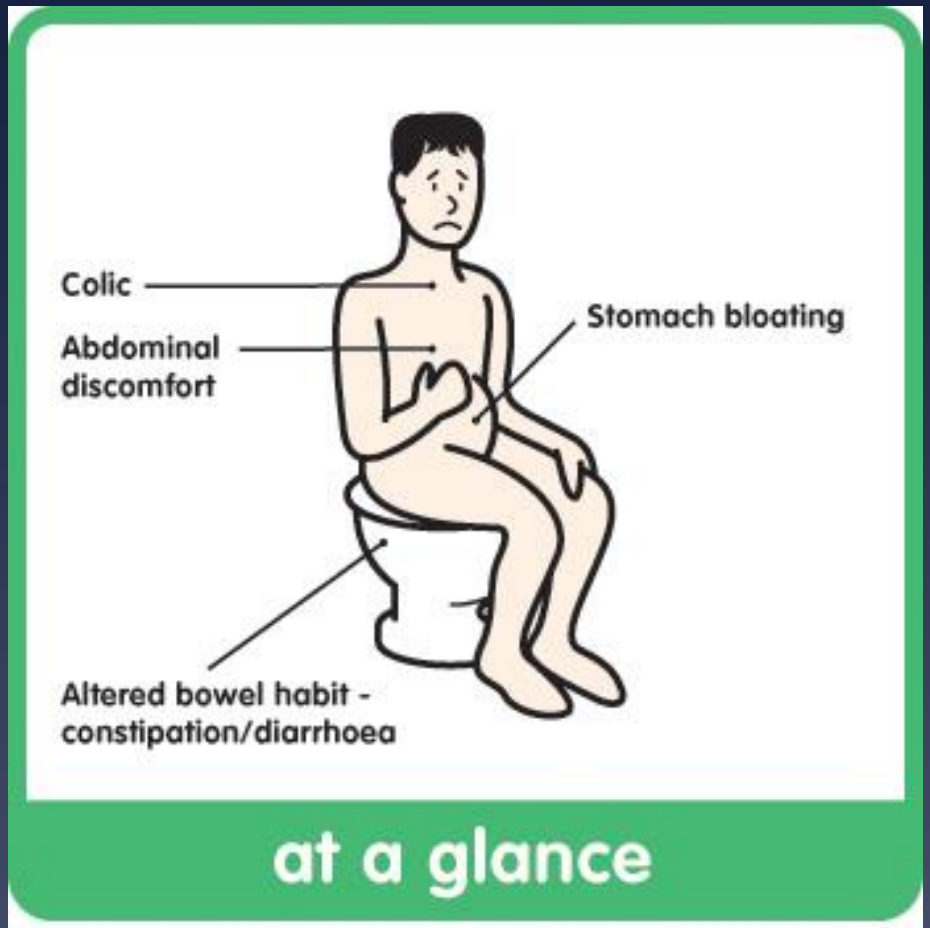
J Gastroenterology Hepatology 2015.

CRC Screening

- Goal: Get people screened
- Many options available
- Consider the discussion detection vs. prevention tests
- Screening does make a difference

Table. Characteristics of Colorectal Cancer Screening Strategies[a]

Screening Method	Frequency[b]	Evidence of Efficacy	Other Considerations
Stool-Based Tests			
gFOBT	Every year	RCTs with mortality end points: High-sensitivity versions (eg, Hemoccult SENSA) have superior test performance characteristics than older tests (eg, Hemoccult II)	Does not require bowel preparation, anesthesia, or transportation to and from the screening examination (test is performed at home)
FIT[c]	Every year		Does not require bowel preparation, anesthesia, or transportation to and from the screening examination (test is performed at home)
FIT-DNA	Every 1 or 3 y[d]		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
Direct Visualization Tests			
Colonoscopy[c]	Every 10 y		Requires less frequent screening Screening and diagnostic follow-up of positive findings can be performed during the same examination
CT colonography[e]	Every 5 y	Test characteristic studies	There is insufficient evidence about the potential harms of associated extracolonic findings, which are common
Flexible sigmoidoscopy	Every 5 y	RCTs with mortality end points: Modeling suggests it provides less benefit than when combined with FIT or compared with other strategies	Test availability has declined in the United States
Flexible sigmoidoscopy with FIT[c]	Flexible sigmoidoscopy every 10 y plus FIT every year	RCT with mortality end point (subgroup analysis)	Test availability has declined in the United States Potentially attractive option for patients who want endoscopic screening but want to limit exposure to colonoscopy



Irritable Bowel Syndrome (IBS)

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.
Ther Adv Gastro 2016.

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

Life Sci 2010.
Gastro 2007.

IBS

- 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

Clin Gastro Hep 2013.
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

IBS

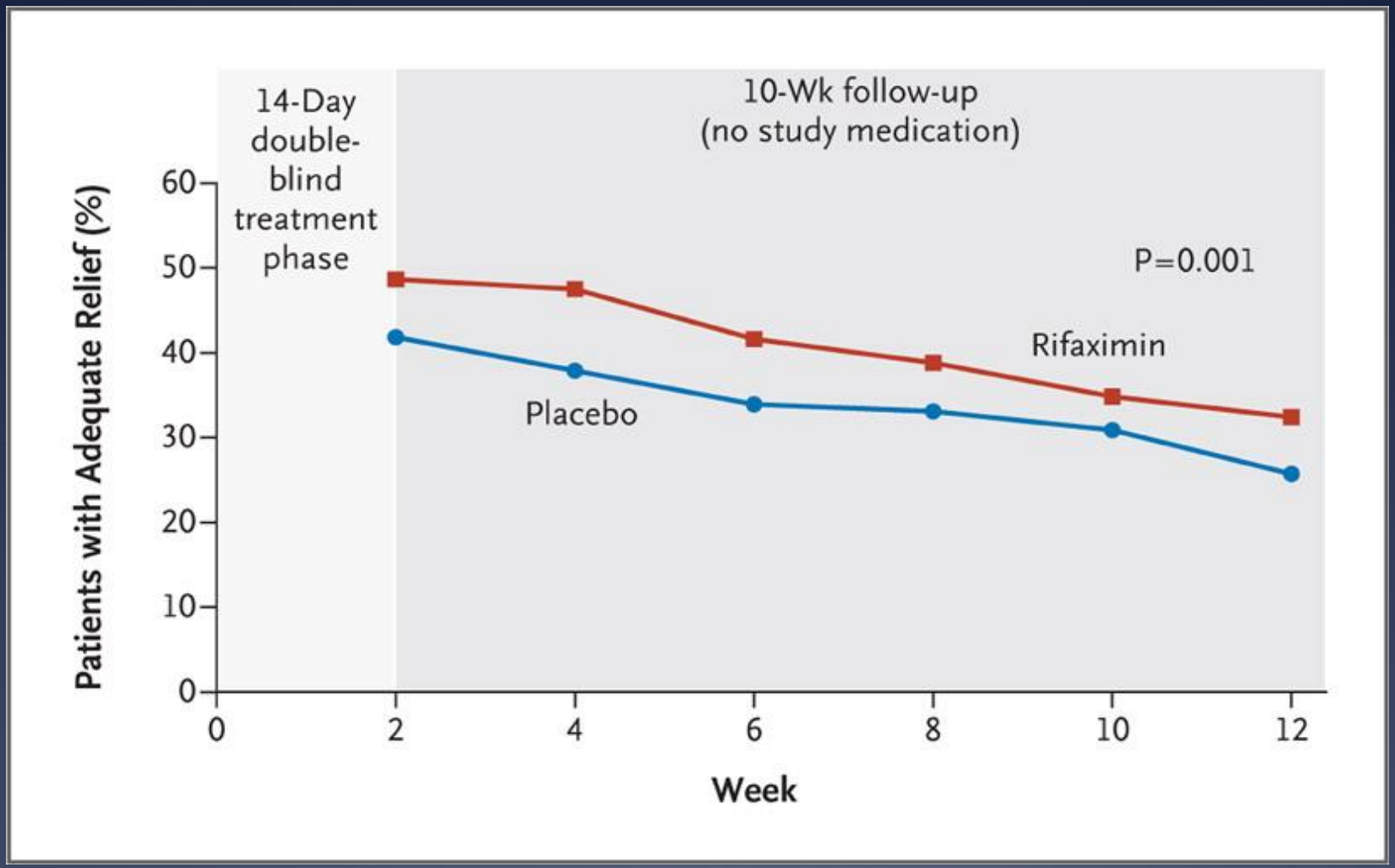
- Rifaximin (Xifaxan)
  - FDA approved:
    - IBS-D - 2015
    - Travelers diarrhea
    - Hepatic encephalopathy
  - Dose for IBS
    - 550mg TID for 2 weeks
  - Expensive

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.



Pimentel M et al. N Engl J Med 2011;364:22-32.

The NEW ENGLAND JOURNAL of MEDICINE

IBS

- 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.

IBS

- 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.
Ther Adv Gastro 2016.

IBS

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

Ther Adv Gastro 2016.

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.
Dig Dis Sci 2015.

Clostridium difficile

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

Epidemiology

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

Janka, J. Clostridium Difficile: current perspectives. Current Opinion in Critical Care. 2009, April 15(2): 149-53.
Kelly, C. Clostridium difficile – more difficult than ever. NEJM. 2008; 359: 1932-40.

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

Janka, J. Clostridium Difficile: current perspectives. Current Opinion in Critical Care. 2009, April 15(2): 149-53.
*Warny, M et al. Toxin production by an emerging strain of Clostridium difficile associated with outbreaks of severe disease in North America and Europe. Lancet 2005; 366:1079.
**Loo, V et al. A predominantly clonal multi-institutional outbreak of Clostridium difficile-associated diarrhea with high morbidity and mortality. NEJM 2005; 353: 2442-9.

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%

Janka, J. Clostridium Difficile: current perspectives. Current Opinion in Critical Care. 2009, April 15(2): 149-53.
Kelly, C. Clostridium difficile – more difficult than ever. NEJM. 2008; 359: 1932-40.

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

Johnson, S. Recurrent Clostridium difficile infection: A review of risk factors, treatments, and outcomes. Journal of infection 2009 (58); 403-410.
Maroo, S et al. Recurrent Clostridium difficile. Gastro 2006 (103): 1311-16.

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

Johnson, S. Recurrent Clostridium difficile infection: A review of risk factors, treatments, and outcomes. Journal of infection 2009 (58); 403-410.
Kelly, C. Clostridium difficile – more difficult than ever. NEJM. 2008; 359: 1932-40.
*Pepin J, et al. Management and outcomes of a first recurrence of Clostridium difficile-associated disease in Quebec, Canada. Clin Infect Dis 2006;42:758-64.

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

Leffler, D. Treatment of Clostridium difficile-Associated Disease. Gastro 2009;136:1899-1912.

Table 3. Treatment of Recurrent *C difficile* Infection

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

Treatment

- 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

Petschow et al. Clin Exp Gastro. 2014

Treatment

- 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

Leffler, D et al. Journal of infection 2009; 58: 403-410.
*Aas, J et al. Clin Infect Dis 2003;26:580-5.
**Sonia, S et al. Journ Clinical Gastro. May 2010.

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

JAMA. Oct 2014.

Conclusions

- CRC
  - Screening is the goal
- IBS
  - New therapeutics
- C-diff
  - Changing landscape
  - FMT

Questions?