REFRACTORY C. DIFFICILE

SMALL GROUP SESSION | CDDW 2020

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CanMEDS Roles Covered

SCMD Semaine canadienne des maladies digestives[MC] | CDDW Canadian Digestive Diseases Week™

X	Medical Expert (as 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.)
X	Communicator (as Communicators, physicians form relationships with patients and their families that facilitate the gathering and sharing of essential information for effective health care.)
	Collaborator (as Collaborators, physicians work effectively with other health care professionals to provide safe, high-quality, patient-centred care.)
X	Leader (as 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.)
	Health Advocate (as 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.)
X	Scholar (as Scholars, physicians demonstrate a lifelong commitment to excellence in practice through continuous learning and by teaching others, evaluating evidence, and contributing to scholarship.)
X	Professional (as 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.)

Conflict of Interest Disclosure

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(Over the past 24 months)
Name: Ted Steiner

Commercial or Non-Profit Interest	Relationship
Verity	Advisory Board
Avir	Advisory Board
Merck	Research Funding
Rebiotix	Research Funding
Seres	Research Funding
Nubiyota	Research Funding
Sanofi Pasteur	Research Funding
Summit	Research Funding

Conflict of Interest Disclosure

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(Over the past 24 months)
Name: Nikhil Pai

Commercial or Non-Profit Interest	Relationship
Abbvie	Advisory Board
Janssen	Advisory Board
Ferring	Advisory Board
Nestle	Advisory Board
Rebiotix	Research Support (materials in kind)

BRIEF OBJECTIVES AND INTERACTIVE DISCUSSION

Describe challenging adult and paediatric cases of rCDI

Review clinical and laboratory definitions for rCDI

Discuss the antibiotic treatment approach for management

Discuss the role of fecal microbiota transplant in management

CHALLENGING CASES OF REFRACTORY C DIFFICILE IN ADULT AND PAEDIATRIC MEDICINE

objective 1

CASE #1

- 68 yo woman with previous localized breast cancer and HTN on HCTZ.
- Developed *E. coli* liver abscess from presumed diverticulitis
- Developed CDI after 6 weeks home IV

Relapse 1	5d after vancomycin course
Relapse 2	10d after vancomycin course → taper
Relapse 3	Longer taper (to q2d)
Relapse 4	Taper to 125mg OD, then FMT

CASE #1 (CONT'D)

FMT #1 via enema

- Diarrhea/cramps on day 6

FMT #2 the following day (no vancomycin)

- Improved for 1d, then worse again
- Cramping and blood in stools intermittently (Christmas)
- Spontaneously stabilized/improved but still having diarrhea

Brought in for FMT #3 (Day 22)

- Grossly bloody stool, no fever, not septic — given FMT
- Checked CBC: WBC = 22k
- Checked stool test: returned PCR+

CASE #1 (CONT'D)

- Patient reported low improvement
- Brought in for FMT #4 on day 30
  - Repeat CBC: WBC = 14
  - I'll check her K+ just in case
- Alert lab call 8 PM: K+ = 1.9
- Given IV K+ and then oral K+ and cholestyramine
- Over the next 2 weeks: gradual improvement in BMs
  - First solid stool on day 39
- Diarrhea completely resolved at next contact

QUESTIONS ABOUT CASE?

DIFFERENCES IN APPROACH

CONSIDERATIONS

CHALLENGES

CASE #2: ACUTE CDI INFECTION IN PREVIOUSLY HEALTHY 2YO BOY

- 2.5yo male referred to ED by pediatrician
- Presented with 7wks hematochezia
- Poor weight, height gain x 6mo
- Stool cultures sent by paediatrician: CDI +ve (PCR)
- Treated with Flagyl x 10d, no improvement
- Treated with 2nd course of Flagyl → bowel movements decreased (12x → 4x/day)
- Ongoing bleeding

CASE #2: ACUTE CDI INFECTION IN PREVIOUSLY HEALTHY 2YO BOY

INVESTIGATIONS IN HOSPITAL

- January 31st: CDI (LAMP) –ve
- Meckel's scan negative
- Hgb 70, CRP 2.3, albumin 30

- February 10th: CDI (LAMP) +ve
- Paediatric ID: 14d of Vancomycin
- February 26th: Hematochezia resolved, formed stools
- Hematochezia recurred 7d after Vanco discontinued
- Mar 12th: CDI (LAMP) +ve

- Decision for EGD/Colonoscopy

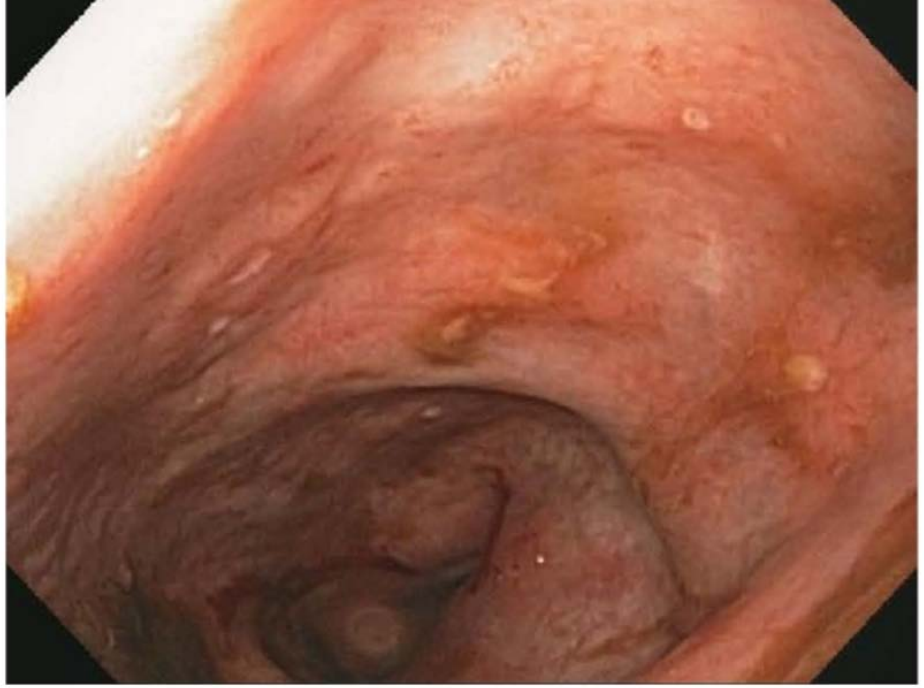
CASE #2: ACUTE CDI INFECTION IN PREVIOUSLY HEALTHY 2YO BOY

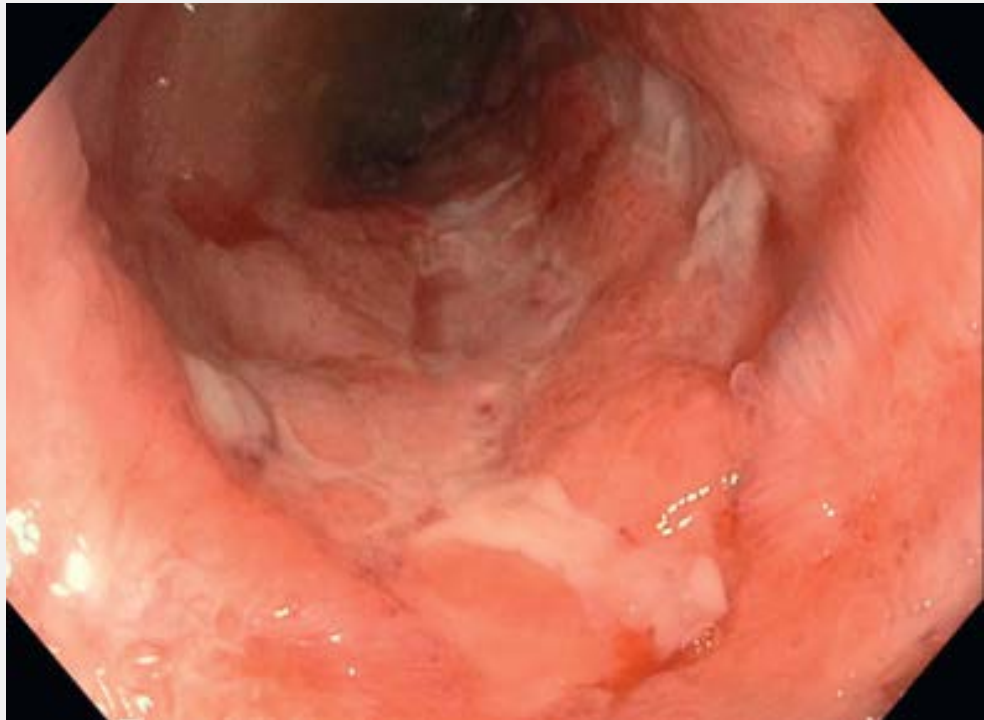
"*Chronic active colitis* noted throughout colon, in absence of granulomas. *Patchy involvement of terminal ileum*. Features of pseudomembranous colitis not evident."

Diagnosis: IBD-Unclassified (favoring Crohn's)

Corticosteroids → 5-ASA → Infliximab 10mg/kg q6wk
Complete biological, clinical remission

CDI (LAMP) still positive





Images from: https://www.sciencedirect.com/science/article/pii/B9780323415095000384
https://www.researchgate.net/publication/223986858_The_Valuable_Role_of_Endoscopy_in_Inflammatory_Bowel_Disease

QUESTIONS ABOUT CASE?

ADDITIONAL QUESTIONS

DIFFERENCES IN APPROACH

CONSIDERATIONS, CHALLENGES

DIAGNOSING REFRACTORY C. DIFFICILE: CLINICAL & LABORATORY DEFINITIONS

objective 2

DEFINING RECURRENT, REFRACTORY RCDI BASED ON RESPONSE TO THERAPY

- Three or more episodes of mild-moderate CDI + failure of 6-8wk taper with vancomycin with or without alternative antibiotic

- Moderate –to-severe CDI not responding to standard therapy for at least a week

Kelly CR, Kim AM, Laine L, Wu GD. The AGA's Fecal Microbiota Transplantation National Registry: An Important Step Toward Understanding Risks and Benefits of Microbiota Therapeutics. Gastroenterology. 2017;152(4):681-684.

VARIETY OF DIFFERENT TESTS AVAILABLE FOR DIAGNOSIS

- 2 primary categories of tests
- Differ in terms of specificity, and sensitivity
- SPECIFIC: Detect free toxin (*C. difficile toxin A & B*)
- SENSITIVE: Detect organisms with potential to produce toxin *in vivo*

TEST	SENSITIVITY	DETECTION	COMMENT
NAAT	High	Toxin gene detection	Highly sensitive and specific for toxigenic CDI; rapid turnaround time
GDH	High	Detection of common antigens in detection of toxigenic and nontoxigenic CDI strains	Highly sensitive for CDI but nonspecific for toxigenic/nontoxigenic strains; rapid turnaround time
EIA toxin A/B	Low	Detection of free toxin	Highly specific for toxigenic CDI but less sensitive than NAAT; rapid turnaround time
CCCNA or TC	High	Detection of free toxin and culture of a toxigenic CDI stain, respectively	Significant labor requirements and long turnaround time; primarily limited to research use

CCCNA = cell culture cytotoxicity neutralization assay; EIA = enzyme immunoassay; GDH = glutamate dehydrogenase; NAAT = nucleic acid amplification test; TC = toxigenic culture

Addendum for: Fecal Microbiota Transplantation for Recurrent Clostridium difficile Infection and Other Conditions in Children: A Joint Position Paper From the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition. J Pediatr Gastroenterol Nutr. 2020;70(3):404.

CHALLENGING TO CLINICALLY DIAGNOSE

KEY PRINCIPLES:

- Symptomatic patient with unformed stool samples
- Other infectious etiologies of diarrhea assessed and ruled out

CLINICAL CHALLENGES:

- Asymptomatic carriage versus acute infection
  - Will be particularly concerning when multiplex panels become primary method of stool testing
- IBD flare versus infectious colitis
- Defining role of C. diff in patients who have symptoms while on low-dose or suppressive vancomycin

WHAT DIAGNOSTIC OPTIONS ARE AVAILABLE IN YOUR PRACTICE?

UNIQUE PEDIATRIC CONSIDERATIONS WHEN DIFFERENTIATING ACUTE VERSUS ASYMPTOMATIC CARRIAGE

- C. difficile may be commensal during infancy → believed to lack toxin receptors (CDI still possible in <1yo if other testing –ve?)
- Colonization, transient carriage, "pass through" rates high
  - Asymptomatic carriage in children with IBD = 17% vs 3% (p=0.012)
- Response to C. difficile-directed Abx not proof of diagnostic accuracy
  - Lack of response to Abx treatment (Vancomycin) → consider other causes of diarrhea

Kubota H, Makino H, Gawad A, et al. Longitudinal Investigation of Carriage Rates, Counts, and Genotypes of Toxigenic Clostridium difficile in Early Infancy. Appl Environ Microbiol. 2016;82(19):5806-14.
Leffler DA, Lamont JT. Clostridium difficile infection. N Engl J Med. 2015;372(16):1539-48.
Leibowitz J, Soma VL, Rosen L, Ginocchio CC, Rubin LG. Similar proportions of stool specimens from hospitalized children with and without diarrhea test positive for Clostridium difficile. Pediatr Infect Dis J. 2015;34(3):261-6.
Hourigan SK, Chirumamilla SR, Ross T, et al. Clostridium difficile carriage and serum antitoxin responses in children with inflammatory bowel disease. Inflamm Bowel Dis. 2013;19(13):2744-52.

EPIDEMIOLOGY OF C. DIFFICILE INFECTION IN CHILDREN

- Multicentre (n=22) study of hospitalized pediatric patients in US, 2001-2006: doubling of incidence in CDI
- 70-80% of pediatric CDI cases community associated
- 3x more common than healthcare-associated CDI
- Prevalence of CDI in children with IBD 46/1000 vs 4.1/1000

RISK FACTORS
Prior antibiotic use
Recent surgery
Malignancy
Solid organ transplant
Tracheostomy or gastrostomy
Acid suppression
Concomitant use of non-CDI antibiotics during CDI treatment
≥1 complex chronic condition

Kim J, Smathers SA, Prasad P, Leckerman KH, Coffin S, Zaoutis T. Epidemiological features of Clostridium difficile-associated disease among inpatients at children's hospitals in the United States, 2001-2006. Pediatrics. 2008;122(6):1266-70.
Wendt JM, Cohen JA, Mu Y, et al. Clostridium difficile infection among children across diverse US geographic locations. Pediatrics. 2014;133(4):651-8.
Hourigan SK, Oliva-hemker M, Hutfless S. The prevalence of Clostridium difficile infection in pediatric and adult patients with inflammatory bowel disease. Dig Dis Sci. 2014;59(9):2222-7.

THE USE AND TIMING OF ANTIBIOTICS IN REFRACTORY C. DIFFICILE TREATMENT

objective 3

"REFRACTORY" RCDI

- Failure to respond to vancomycin or FMT
  - No high-level vancomycin resistant *C. difficile*
  - Patient with fulminant CDI may not respond: role for urgent surgery
- Things to rule out:
  - non-CDI colonization with IBS
  - microscopic colitis
  - diarrhea due to vancomycin
  - IBD
- Switching to fidaxomicin or high-dose vancomycin seldom of any benefit
- Refer to GI for assessment

20-30% OF CASES WILL HAVE RECURRENCE WITHIN DAYS-WEEKS AFTER ABX

Potential etiologies for failed treatment:

- Continued C. difficile exposure
- Persistent dysbiosis
- Lack of protective immune response to CD toxins?

Recognized risk factors:

- Abx use
- Older age
- Severity of initial CDI episode

Kociolek LK, Gerding DN. Breakthroughs in the treatment and prevention of Clostridium difficile infection. Nat Rev Gastroenterol Hepatol. 2016;13(3):150-60.

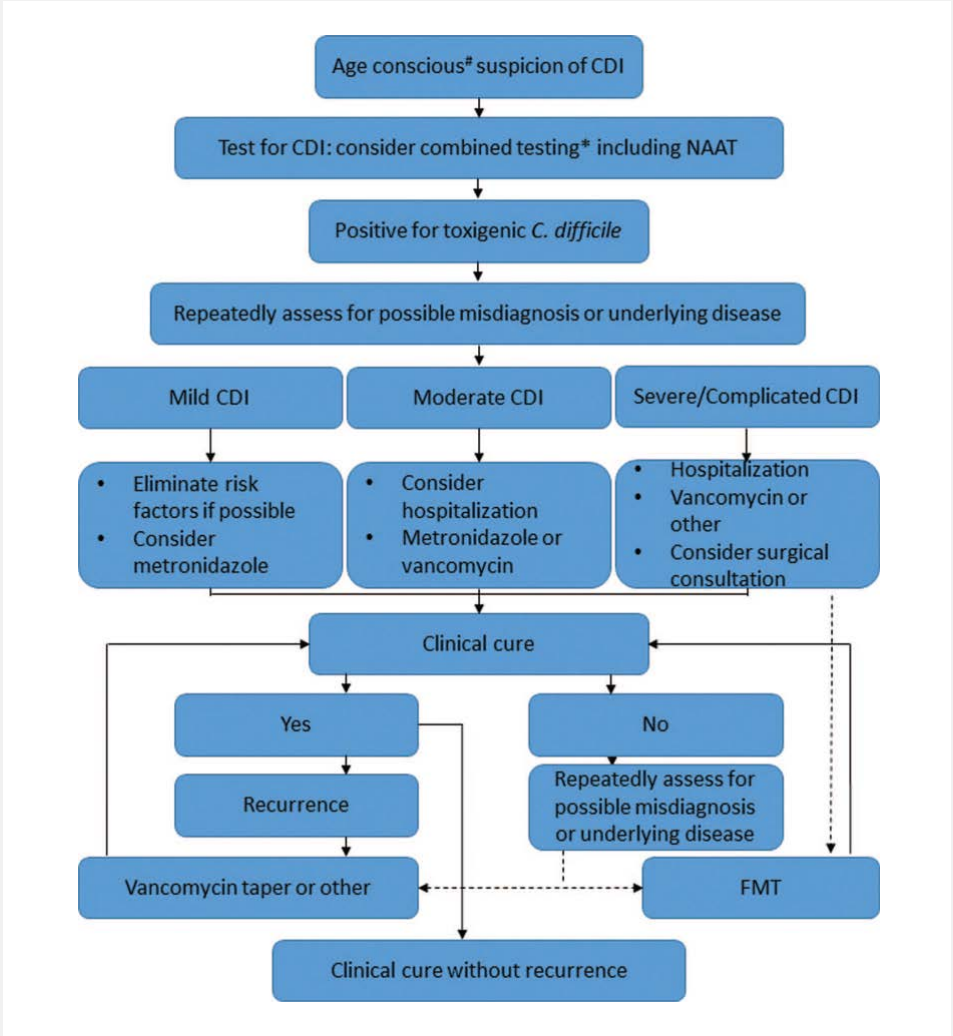
TREATMENT ALGORITHM OFFERS STEPWISE APPROACH TO PEDIATRIC CDI

Oral metronidazole for first episode, and first recurrence of mild or moderate CDI

Vancomycin for first recurrence in high-risk children OR first-line for moderately ill hospitalized patients (particularly with comorbidities)

If response, consider Vancomycin taper +/- FMT

If no response, consider alternate diagnosis, or underlying disease +/- FMT



Davidovics ZH, Michail S, Nicholson MR, et al. Fecal Microbiota Transplantation for Recurrent Clostridium difficile Infection and Other Conditions in Children: A Joint Position Paper From the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition. J Pediatr Gastroenterol Nutr. 2019;68(1):130-143.

FROM AMMI GUIDELINES (2018)

Table 2: Treatment recommendations for *Clostridium difficile* infection (CDI) in adults

Clinical definition	Parameters	Treatment recommendations
Initial episode		
Mild to moderate	• WBC* $\leq 15.0 \times 10^9$/L, and • Serum creatinine $\leq 1.5 \times$ baseline	First line: • Vancomycin 125 mg po QID for 10–14 days Alternative Choices: • Fidaxomicin 200 mg po BID for 10 days • Metronidazole 500 mg po TID for 10–14 days can be used in patients with mild diarrhea when the costs of vancomycin or fidaxomicin may be prohibitive for their use.
Severe, uncomplicated†	• WBC* $> 15.0 \times 10^9$/L or • Serum creatinine $> 1.5 \times$ baseline • Hypoalbuminemia	• Vancomycin 125 mg po QID for 10–14 days, or • Fidaxomicin 200 mg po BID for 10 days
Severe, complicated	• Hypotension or shock, ileus, megacolon	• Vancomycin 125–500 mg po QID for 10–14 days or via nasogastric tube in conjunction with intravenous metronidazole 500 mg Q 8 H • Alternative: Fidaxomicin 200 mg po BID for 10 days with intravenous metronidazole 500 mg Q 8 H if severe allergy to oral vancomycin • If paralytic ileus is present, consider administering vancomycin rectally 500 mg in approximately 100 mL normal saline per rectum every 6 hours as a retention enema, in conjunction with intravenous metronidazole 500 mg Q 8 H and oral vancomycin

Loo VG, David I, Embil J, et al. Association of Medical Microbiology and Infectious Disease Canada treatment practice guidelines for Clostridium difficile infection. Journal of Association of Medical Microbiology and Infectious Disease Canada. 3. 71-92.

Recurrent episodes		
First recurrence, mild to moderate	• WBC* $\leq 15.0 \times 10^9$/L, and • Serum creatinine ≤ 1.5 baseline	First line: • Vancomycin 125 mg po QID for 14 days Alternative choices: • Fidaxomicin 200 mg po BID for 10 days • Metronidazole 500 mg po TID for 10–14 days if vancomycin or fidaxomicin cannot be used.
First recurrence, severe, uncomplicated†	• WBC* $> 15.0 \times 10^9$/L, or • Serum creatinine $> 1.5 \times$ baseline • Hypoalbuminemia	• Vancomycin 125 mg po QID for 14 days, or • Fidaxomicin 200 mg po BID for 10 days
Second or subsequent recurrences		• Vancomycin as a prolonged tapered and/or pulsed regimen (e.g., 125 mg po QID for 14 days; 125 mg po TID for 7 days; 125 mg po BID for 7 days; 125 mg po once daily for 7 days, and then every 2 or 3 days for 2–8 weeks) • Consider fecal microbiota transplantation for recurrence following a vancomycin taper

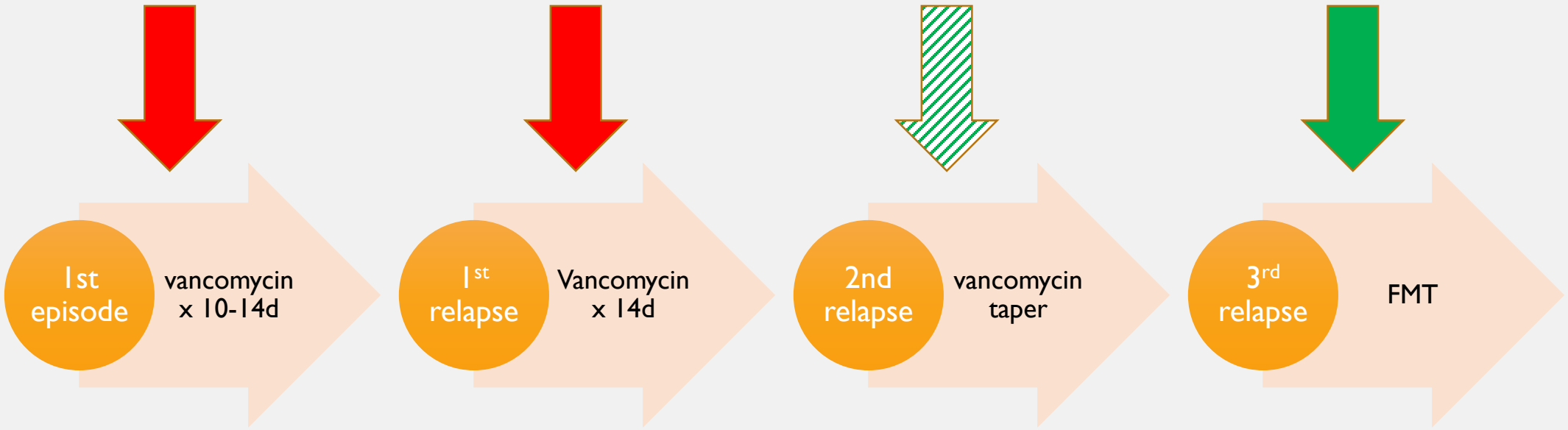
Loo VG, David I, Embil J, et al. Association of Medical Microbiology and Infectious Disease Canada treatment practice guidelines for Clostridium difficile infection. Journal of Association of Medical Microbiology and Infectious Disease Canada. 3. 71-92.

WHAT APPROACH TO TREATMENT DO YOU FOLLOW IN YOUR PRACTICE?

FECAL MICROBIOTA TRANSPLANT IN REFRACTORY C. DIFFICILE TREATMENT

objective 4

WHEN IS THE RIGHT TIME FOR FMT?



SUMMARY OF FMT STUDIES FOR CDI

	Van Nood	Cammarota	Youngster	Lee	Kelly	Hota	Kao
Number of patients	16	20	20	178	22	16	116
Route of admin	Lavage then ND* tube	Colonoscopy	NG-10 Colonoscopy-10	Enema	Colonoscopy	Enema	Lavage then capsule vs. C-scope
FMT type	Fresh	Fresh	Frozen	Fresh vs. Frozen	Fresh	Fresh	Frozen
Follow-up (weeks)	10	10 weeks after last infusion	8	13	8	17	12
No. of FMTs/ Response rate (%)	1(81) 2(93.7)	1 (65) ≥2 (90)	1 - NG (60) 1 – CS (80) 2 -NG/NG (80) 2- CS/NG (100)	1(62) 2 (84)	1 (91)	1 (41.7)	1 (96% in each arm)

QUESTIONS FOR FMT?

- Pretreat with vancomycin or not?
  - Receipt of Vancomycin taper associated with success in multivariate model
  - Improves patient comfort and tolerability
- When to stop vancomycin?
  - Vancomycin at inhibitory concentrations in stool 4-6d after treatment
  - Relapses typically not before 5d
  - Unclear how long it takes for FMT to "take"
  - Most people stop 48h pre-FMT

Clin Infect Dis. 2017 Oct 1;65(7):1214-1217
PLoS One. 2013 Oct 2;8(10):e76269

OTHER FMT QUESTIONS

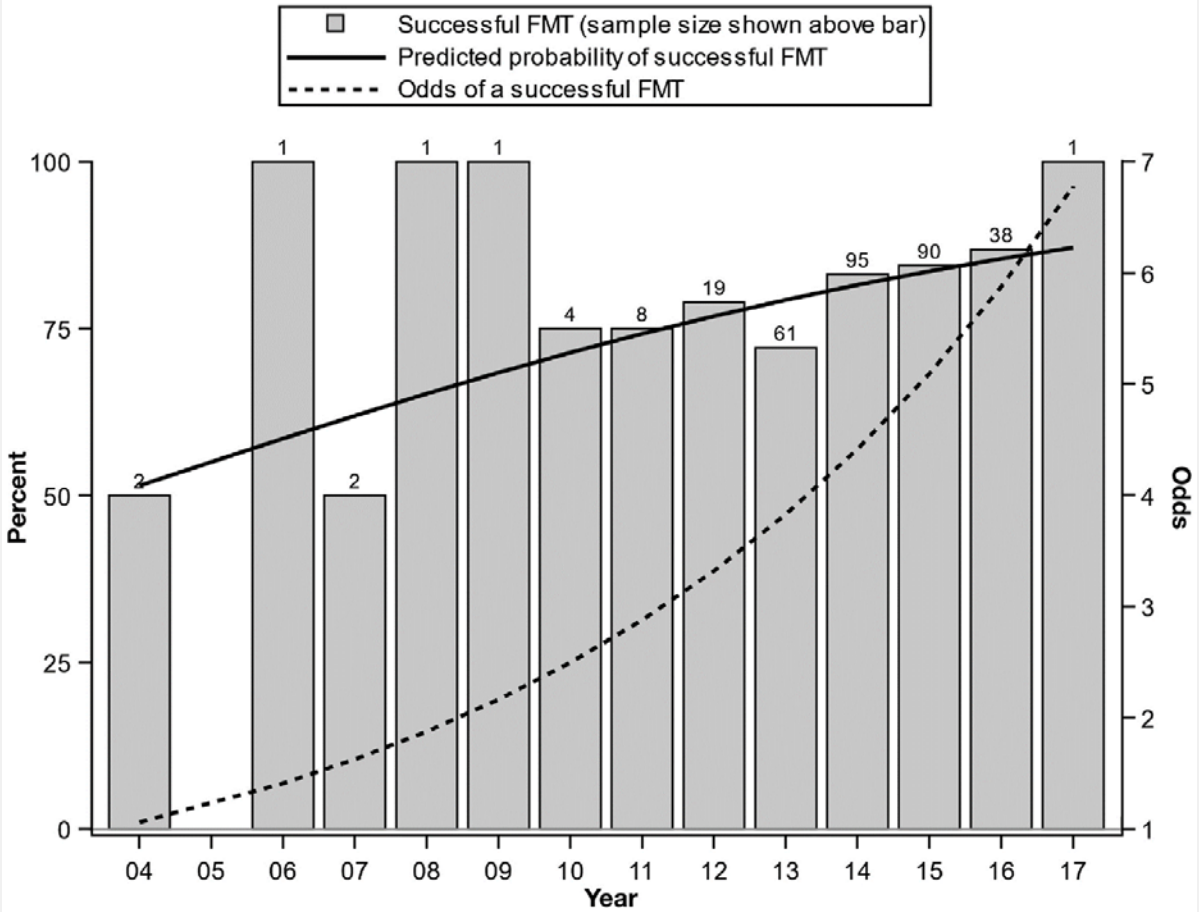
- Bowel lavage?
  - May reduce intestinal vancomycin concentrations
  - "CTRL+ALT+DEL" for the gut?
  - Osmotic effects can strip colonic mucus and cause dysbiosis
- Probiotics?
  - No evidence of benefit
  - May inhibit microbial restitution

Cell. 2018 Jun 14;173(7):1742-1754 PLoS One. 2013 Oct 2;8(10):e76269
Cell 2018 Sep 6;174(6):1406-142

FMT IS SIMILARLY EFFECTIVE FOR RCDI IN PAEDIATRICS

- Less experience in paediatrics
- Multicenter, *n*=355 children
- 81% response x 1 FMT
  87% response x 1-2 FMT

- 2.5% risk of IBD flare
- 4.8% risk of SAE
- Each successive year greater likelihood of successful FMT (experience matters!)



Percentage of successful FMT by year. Shown above each bar is the total number of subjects with FMT per year.

Nicholson MR, Mitchell PD, Alexander E, et al. Efficacy of Fecal Microbiota Transplantation for Clostridium difficile Infection in Children. Clin Gastroenterol Hepatol. 2020;18(3):612-619.e1.

FMT FOR RCDI SAFE IN IMMUNOCOMPROMISED PATIENTS

- Systematic review (44 studies, *n*=303)
- 77.2% on immunosuppressants
- 19.2% ≥1 immunocompromising condition

- Rate of SAEs similar in immunocompetent hosts
- Difficult to discern contribution of treatment from condition

SAE	Diagnosis	Comments
Death (2)	Organ Transplant (2)	1. 13d after FMT d/t pneumonia 2. 1d after FMT d/t aspiration during sedation for colonoscopy
Colectomy (2)		
Bacteremia (5)		
Hospitalization (10)		Following FMT administration
IBD Flares (7)	IBD	
Life-Threatening (7)		Not otherwise specified

Shogbesan O, Poudel DR, Victor S, et al. A Systematic Review of the Efficacy and Safety of Fecal Microbiota Transplant for Infection in Immunocompromised Patients. Can J Gastroenterol Hepatol. 2018;2018:1394379.

IBD AFFECTS OUTCOME OF FMT IN IBD

	rCDI alone (n=229)	rCDI + IBD (n=43)	*p value*
Age (mean ± SD)	60.8 ± 17.3	38.8 ± 17.9	<0.0001
Female gender	73%	51%	0.0065
IBD		UC: 21 CD: 22	
BM 24hrs pre FMT	5.2 ± 4.6	8.3 ± 7.2	0.0044
Success after 1 FMT	92%	75%	0.0018
Success after ≥2 FMT	99%	83%	
IBD flare post FMT		11 (25%)	

Khoruts A, Rank KM, Newman KM, et al. Inflammatory Bowel Disease Affects the Outcome of Fecal Microbiota Transplantation for Recurrent Clostridium difficile Infection. Clin Gastroenterol Hepatol. 2016;14(10):1433-8.

APPROACH TO FMT IN ADULT PATIENTS WITH IBD

- Get them as close as possible to asymptomatic first
  - Maximize IBD treatment and vancomycin
  - Do not withhold biologics or steroids
- Taper vancomycin to lowest tolerated dose
- Administer 2-3 FMT doses over a period of 1 week
- Warn about risk of disease flare after FMT in patients who are in IBD remission
- If symptoms recur: test again for CDI → no test of cure

THANK YOU FOR YOUR ATTENTION

PAEDIATRIC FMT RESEARCH PROGRAM

MCMASTER UNIVERSITY | DEPARTMENT OF PEDIATRICS | DIVISION OF GI & NUTRITION

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