Clostridium Difficile Colitis: Treatments, Guidelines, and Challenges

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University of Pittsburgh
Chief, Trauma and Acute Care Surgery
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Acting Chief, General Surgery, VA Pittsburgh Healthcare System
Background

- *Clostridium difficile*: anaerobic, gram positive, spore forming, bacillus

- Up to 3 million cases per year in US

- Estimated $3.2 billion/year in expenditures

- Mortality estimated to be ~4-8%
Background
- Oral ingestion of *C. difficile* spores

- Resistant to gastric acidity (low inoculum required)
- **C. difficile** colonizes the colon after the normal gut microflora is disrupted by antibiotics or other host factors.

- Kyne et al demonstrated that 31% of patients who received antibiotics in the hospital were colonized with **C. difficile** and 56% of these developed symptomatic disease.
Clostridium difficile Colitis

Pseudomembranous colitis

Large intestine (colon)

Clostridium difficile bacteria

Intestinal lining
BI/NAP1/027: hypervirulent strain

An Epidemic, Toxin Gene–Variant Strain of *Clostridium difficile*

L. Clifford McDonald, M.D., George E. Killgore, Dr.P.H., Angela Thompson, M.M.Sc.,
Robert C. Owens, Jr., Pharm.D., Sophia V. Kazakova, M.D., M.P.H., Ph.D., Susan P. Sambol, M.T.,
Stuart Johnson, M.D., and Dale N. Gerding, M.D.

-More than 60% of isolates at UPMC
Risk Factors

- Antibiotic use (fluoroquinolones, 2nd & 3rd generation cephalosporins, clindamycin, & β-lactams)
- Hospitalization (20-40% patients colonized)
- Advanced age
- Immunosuppression
- Antacids (PPI and H₂ blockers)
- GI surgery, IBD, NPO, elemental diets, NG tubes
Signs/Symptoms

- Diarrhea
- Abdominal Cramps/Pain
- Leukocytosis
- Fever
- End or...
Issues

- Who to operate on? What are the indications for operative management? When to operate?

- What operation?

- What can we improve upon?
An ounce of prevention.....

- Infection Control

- Isolation precautions
- Handwashing
- Barrier precautions
- Cleaning with bleach
- Antibiotic stewardship
Severity Scoring and Treatment

Mild diarrhea

Sepsis/Extremis
Severity Scoring and Treatment

- Mild diarrhea
- Sepsis/Extremis
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<tr>
<th>Severity</th>
<th>Criteria</th>
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<tr>
<td>Mild or Moderate:</td>
<td>WBC of 15K or lower &amp; Serum creatinine &lt;1.5 times pre-morbid level</td>
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<td>Severe:</td>
<td>WBC of 15K or higher or Serum creatinine &gt;1.5 times the premorbid level</td>
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<td>Severe, Complicated:</td>
<td>Hypotension or shock, ileus, megacolon</td>
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-SHEA and IDSA Clinical Practice Guidelines 2010
Practice Guidelines

The American Journal of Gastroenterology, (26 February 2013) | doi:10.1038/ajg.2013.4

Guidelines for Diagnosis, Treatment, and Prevention of Clostridium difficile Infections

Christina M Surawicz, Lawrence J Brandt, David G Binion, Ashwin N Ananthakrishnan, Scott R Curry, Peter H Gilligan, Lynne V McFarland, Mark Mellow and Brian S Zuckerbraun
### ACG Severity Scoring and Treatment

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<td>- Serum albumin &lt; 3 g/dL</td>
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<td>- Abdominal tenderness</td>
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Fujitani et al. Comparison of clinical severity score indices for Clostridium difficile infection. *Infect Control Hosp Epidemiol*. 2011
Factors that have been associated with a poor prognosis from CDAD.

Non-modifiable patient factors:
- Age > 65
- Pre-existing renal or pulmonary disease
- Immunosuppression
- High ASA class

Physical exam/clinical findings:
- Fever
- Ileus/distention
- Hypotension/shock requiring vasopressors
- Mental status changes
- Need for intubation/mechanical ventilation

Laboratory values:
- High White Blood Cell count
- Increasing lactate
- Increased creatinine/renal dysfunction
- Low Albumin

CT scan findings:
- Pancolitis/ascites
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  - WBC ≥ 15,000 cells/mm³  
  - Serum albumin < 3 g/dL  
  - Abdominal tenderness    | Vancomycin 125 mg PO qid        |
Metronidazole v. Vancomycin

**Metronidazole**
- Effective as intravenous or enteral form
- Does not reach colon at effective MIC unless diarrhea
- Both dosing regimens dependent upon GI motility

**Vancomycin**
- Intravenous not effective
- Enteral (oral, tube, rectal) reaches colon at effective MIC in both diarrheal and non-diarrheal stool
Metronidazole v. Vancomycin

-No antimicrobial agent is clearly superior for the initial cure of C. difficile infection

-Three randomized control trials have compared metronidazole to vancomycin

*One trial demonstrated vancomycin superior in severe disease (Zar et al, Clinical Infectious Disease, 2007) (evidence considered insufficient)
Novel medical treatment strategies for *Clostridium difficile infection*

**Antibiotics:**
- Fidaxomicin (FDA approved)
  - Rifaximin
  - Nitazoxanide
  - Teicoplanin
  - Ramoplanin

**Immunization therapy:**
- Toxoid Vaccines
- Anti-*Clostridium difficile* toxin antibodies
  - Intravenous immunoglobulin

**Biotherapy:**
- Fecal bacteriotherapy
- Non-toxigenic *Clostridium difficile* strains
  - Probiotics
Fidaxomicin versus Vancomycin for *Clostridium difficile* Infection

Thomas J. Louie, M.D., Mark A. Miller, M.D., Kathleen M. Mullane, D.O., Karl Weiss, M.D., Arnold Lentnek, M.D., Yoav Golan, M.D., Sherwood Gorbach, M.D., Pamela Sears, Ph.D., and Youe-Kong Shue, Ph.D. for the OPT-80-003 Clinical Study Group


- Non-inferior to vancomycin for cure rate
- Lower recurrence rate compared to vanco
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Duodenal Infusion of Donor Feces for Recurrent *Clostridium difficile*

Els van Nood, M.D., Anne Vrieze, M.D., Max Nieuwdorp, M.D., Ph.D., Susana Fuentes, Ph.D., Erwin G. Zoetendal, Ph.D., Willem M. de Vos, Ph.D., Caroline E. Visser, M.D., Ph.D., Ed J. Kuijper, M.D., Ph.D., Joep F.W.M. Bartelsman, M.D., Jan G.P. Tijssen, Ph.D., Peter Speelman, M.D., Ph.D., Marcel G.W. Dijkgraaf, Ph.D., and Josbert J. Keller, M.D., Ph.D.

Duodenal Infusion of Donor Feces for Recurrent Clostridium difficile
U.S.’s first stool bank supplies hospitals with fecal transplants for C. difficile treatment

February 22, 2014 8:00 am by Deanna Pogorelc | 1 Comments
Recommended for recurrent disease

1\textsuperscript{st} Recurrence: Vancomycin

2\textsuperscript{nd} Recurrence: Vancomycin 7 week taper

3\textsuperscript{rd} Recurrence: Fecal Microbiota Therapy
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- Fever $\geq 38.5^\circ$  
- Ileus or significant abdominal distention/tender  
- WBC $\geq 35,000$ cells/mm$^3$  
- Serum lactate levels greater than 2.2 mmol/Liter | **Metronidazole 500 mg IV tid**  
+ **Vancomycin 125 mg PO qid**  
+ **Vancomycin 500 mg in 500 mL saline as enema qid** (if ileus or distended)  
+ **SURGICAL CONSULTATION** |
Role for Surgical Treatment?

Colectomy can be life-saving for selected patients.\textsuperscript{208} Colectomy has usually been performed for patients with megacolon, colonic perforation, or an acute abdomen, but the procedure is now also performed for patients with septic shock.\textsuperscript{208,215} Among patients with a lactate level of 5 mmol/L or greater, postoperative mortality is 75\% or higher, when possible colectomy should be performed earlier.\textsuperscript{208}

\textit{Treatment of recurrent CDI}... The frequency of further...
Colectomy associated with a 35-85% mortality.

Suggests:
- patients are sick
- magnitude of colectomy too significant
- we intervene too late
Surgery and CDAD

Dilemma

• Operate early- near total colectomy + ileostomy is a large operation with significant short-term and long-term consequences.

• Operate early- may end up operating on patients that would not need it.

• Operate once patient sick: too late
Surgery and CDAD

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Surgery and CDAD

With the goal of decreasing mortality...

*Lower the threshold for surgical consultation!*

*DO NOT THINK OF SURGICAL CONSULT AND POSSIBLE SURGICAL MANAGEMENT AS SALVAGE THERAPIES!!!*
A diagnosis of CDAD as determined by one of the following:

1. Positive C Diff test
2. Endoscopic findings
3. CT scan consistent with CDAD

Plus any one of the following criteria:

1. Peritonitis
2. Perforation
3. Worsening abdominal distention/pain
4. Severe Sepsis
5. Intubation
6. Ongoing Vasopressor requirement
7. Mental status changes
8. Unexplained clinical deterioration
9. Renal Failure
10. Lactate > 5mmol/L
11. White blood cell count greater or equal to 50,000
12. Abdominal compartment syndrome
13. Not improving after ? days
Subtotal colectomy is the standard of care

Laparotomy for fulminant pseudomembranous colitis.

Medich DS, Lee KK, Simmons RL, Grubbs PE, Yang HC, Showalter DP.

Department of Surgery, University of Pittsburgh, PA 15261.

Clostridium difficile-associated pseudomembranous colitis is an increasingly common nosocomial infection that usually responds to oral antibiotics. Presentation as an acute abdomen occurred in 12 patients, leading to 14 laparotomies. A distinctive clinical picture was observed: advanced age, recent treatment with antibiotics, fever, abdominal pain, tenderness, marked leukocytosis, and ileus. Only six of the 12 patients had diarrhea. Five were immunosuppressed. Abdominal computed tomographic scans revealed ascites and a massively thickened colonic wall. All four patients treated by subtotal colectomy survived. Four of 10 patients treated only with laparotomy or segmental colectomy died, four responded to medical therapy, and the conditions of two deteriorated but were salvaged by subtotal colectomy. Early diagnosis via endoscopy or computed tomography should obviate the need for exploratory operations. However, progressive toxic effects indicate failure of medical therapy and the need for subtotal colectomy.

PMID: 1524485 [PubMed - indexed for MEDLINE]
Fulminant *Clostridium difficile*: An Underappreciated and Increasing Cause of Death and Complications

Ramsey M. Dallal, MD,* Brian G. Harbrecht, MD,* Arthur J. Boujoukas, MD,† Carl A. Sirio, MD,† Linda M. Farkas, MD,* Kenneth K. Lee, MD, and * Richard L. Simmons, MD*

hosed all patients, whereas 12.5% of toxin assays and 10% of endoscopies were falsely negative. Patients undergoing colectomy for *C. difficile* colitis had an overall death rate of 57%. Significant predictors of death after colectomy were preoperative vasopressor requirements and age.
Not C Diff Colon
Is colectomy necessary for the treatment of severe, complicated (fulminant) CDAD?
Can we offer a procedure that adequately treats severe, complicated CDAD that is less morbid?
Pathophysiology

- *C. difficile* overgrows and produces exotoxins

-Toxins cause mucosal damage and inflammatory cell infiltration.

![Image of mucosal damage](image-url)
Hypothesis: Therapy to decrease bacterial counts and toxin levels throughout the whole colon will adequately treat severe, complicated CDAD.
vancomycin
Hypothesis

Loop ileostomy and colonic lavage followed by post-operative vancomycin flushes is an alternative to colectomy in the treatment of severe, complicated *C. Diff.*
Methods

1. Exploratory laparoscopy/laparotomy
2. Creation of diverting loop ileostomy
3. Colonic lavage with 8 liters of warm PEG3350/balanced electrolyte solution (Go-Lightly™) via ileostomy
4. Post-op antegrade vancomycin flushes via ileostomy (500mg in 500ml tid) for 10 days
Diverting Loop Ileostomy and Colonic Lavage: An Alternative to Total Abdominal Colectomy for the Treatment of Severe, Complicated Clostridium difficile Associated Disease

Neal MD, Alverdy JC, Hall DE, Simmons RL, Zuckerbraun BS

Loop ileostomy/colonic lavage v. total abdominal colectomy (historical controls) for severe, complicated *C. Diff.*

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<td>31.4±9.0</td>
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<td>16/81* (20%)</td>
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<td>Alive at 1 year</td>
<td>54/65 (83%)</td>
<td>30/41 (73%)</td>
</tr>
<tr>
<td>Restoration of GI continuity</td>
<td>46/54 (85%)</td>
<td>7/30 (23%)</td>
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-Loop ileostomy and colonic lavage is an alternative to total abdominal colectomy for the treatment of severe, complicated C. Diff

-Improved survival in our series

-Colon preserved and many patients have had restoration of GI continuity
- Only absolute contraindication to minimally invasive approach is abdominal compartment syndrome.

- Limitation of study is single center data
This approach may prove to be a better alternative to colectomy because:

- Colon is usually viable and can recover.

- Adequately treats the infection and resolves systemic symptoms.
Loop ileostomy/colonic lavage v. total abdominal colectomy (historical controls) for severe, complicated *C. Diff*.

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<td>Time from presentation to surgical consultation</td>
<td>11±9 hours</td>
<td>32±12 hours</td>
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<tr>
<td>Time from surgical consultation to operative intervention</td>
<td>9±6 hours</td>
<td>29±12 hours</td>
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Loop ileostomy/colonic lavage v. total abdominal colectomy

- Is there a patient that is better of with TAC?
- Who is not a candidate for this operation?
Loop ileostomy/colonic lavage v. total abdominal colectomy

-Is there a patient that is better off with TAC?
-Who is not a candidate for this operation?

*Patients with colonic compromise.*
Loop ileostomy/colonic lavage v. total abdominal colectomy

- Is there a patient that is better off with TAC?
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* Patients with colonic compromise.
* Abdominal compartment syndrome.
Loop ileostomy/colonic lavage v. total abdominal colectomy

-Is there a patient that is better off with TAC?
-Who is not a candidate for this operation?

*Patients with colonic compromise.
*Abdominal compartment syndrome.
*Patient population that has done the worse-
  Patients with acute renal failure (anuric, ongoing fluid resusc, requiring hemodialysis.
Figure 1.

Diarrhea and confirmed or suspected CDI

Fluid and electrolyte resuscitation as necessary/Infection control measures/stop inciting antibiotics if possible

Mild/moderate Disease

- Metronidazole 500 mg PO tid for 10 days

Severe Disease

- Vancomycin 125 mg PO qid For 10 days

Severe, Complicated Disease

- Surgical consultation/CT scan abdomen/pelvis

Daily assessment

- If symptoms not resolving within 6 days: Surgical consultation, CT scan

If worsening clinical symptoms or deterioration, worsening WBC, cardiopulmonary compromise, or end organ failure

- Metronidazole 500 mg IV tid Plus
  - Vancomycin 125 mg PO qid Plus
  - Vancomycin 500 mg in 500 mL enema

Yes

OPERATIVE MANAGEMENT
OPERATIVE MANAGEMENT STRATEGY FOR CDAD

Does the patient have abdominal compartment syndrome?

(≈5% incidence) yes

Exploratory laparotomy, subtotal abdominal colectomy with end ileostomy.

No

Exploratory laparoscopy (convert to laparotomy as necessary)

Colonic perforation/necrosis?

Yes (rare)

Loop ileostomy/intraoperative colonic lavage

No

Development of abdominal compartment syndrome post-op?

Yes

(≈7% incidence; Usually within 48 hours)

No

Monitor for continued improvement