Clostridium Difficile Colitis: Treatments, Guidelines, and Challenges

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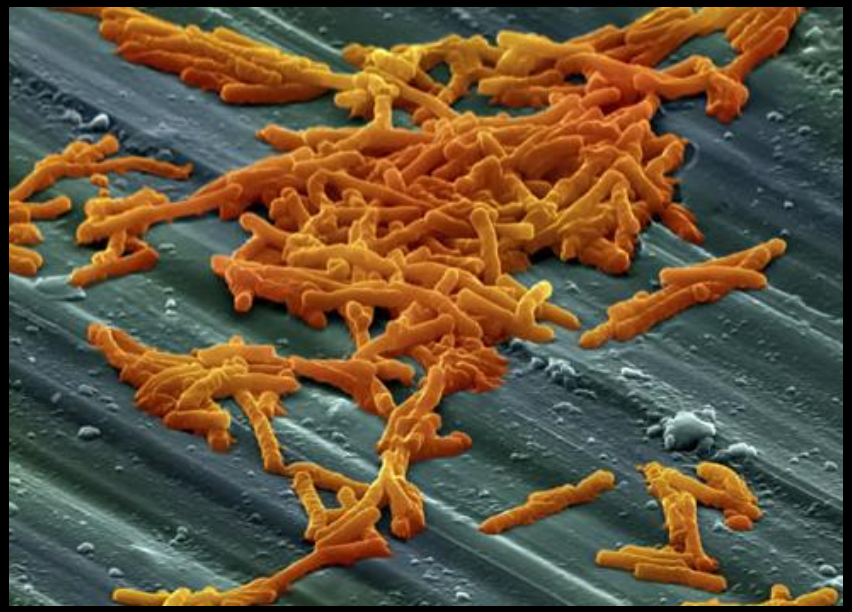
Background

-*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

From Medscape Medical News

C Difficile Surpasses MRSA as the Leading Cause of Nosocomial Infections in Community Hospitals

Emma Hitt, PhD

Medscape Medical News

Pathophysiology

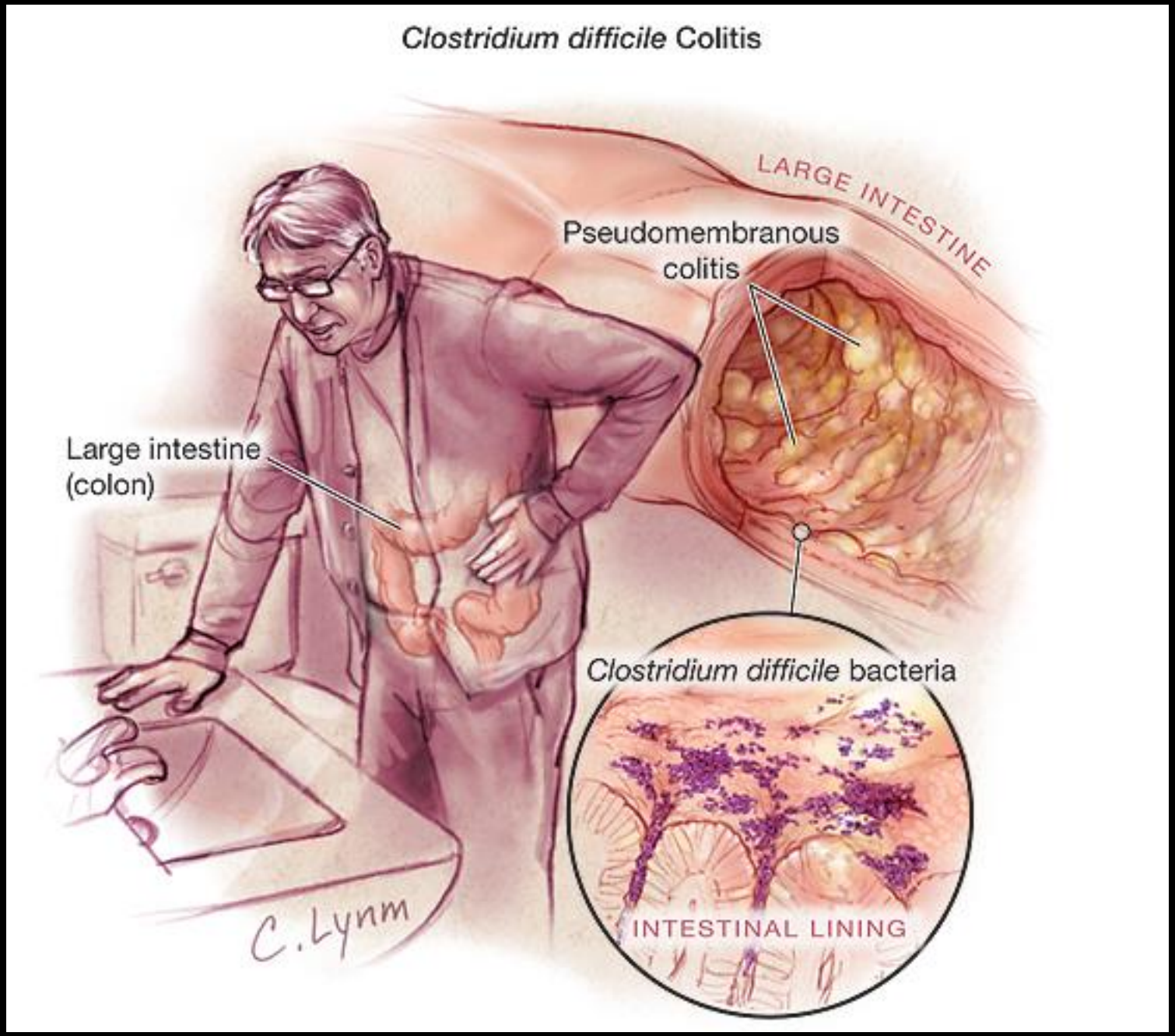
-Oral ingestion of *C. difficile* spores

-Resistant to gastric acidity (low inoculum required)

Pathophysiology

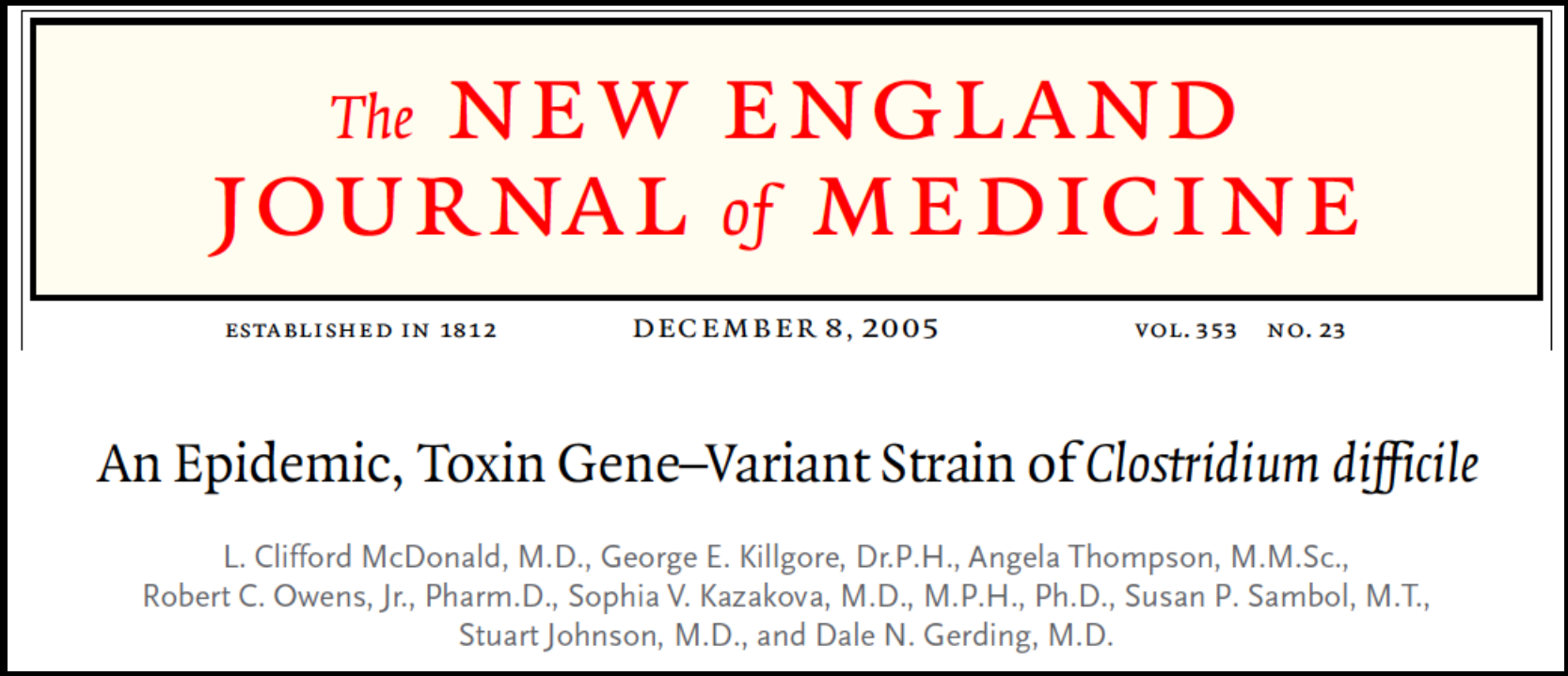
-*C. difficile* colonizes the colon after the normal gut microflora is disrupted by antibiotics or other host factors.

-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
LARGE INTESTINE
Pseudomembranous colitis
Large intestine (colon)
Clostridium difficile bacteria
INTESTINAL LINING
C.Lynm

Pathophysiology

BI/NAP1/027: hypervirulent strain



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 DECEMBER 8, 2005 VOL. 353 NO. 23

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

-Immunosuppresion

-Antacids (PPI and H_2 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?

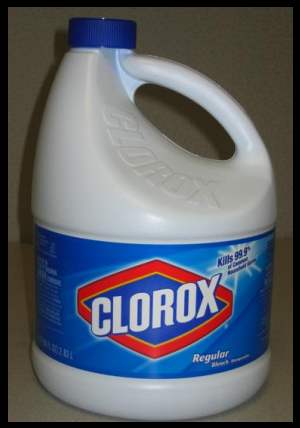
-What operation?

-What can we improve upon?

An ounce of prevention…..

-Infection Control

- Isolation precautions
- Handwashing
- Barrier precautions
- Cleaning with bleach
- Antibiotic stewardship

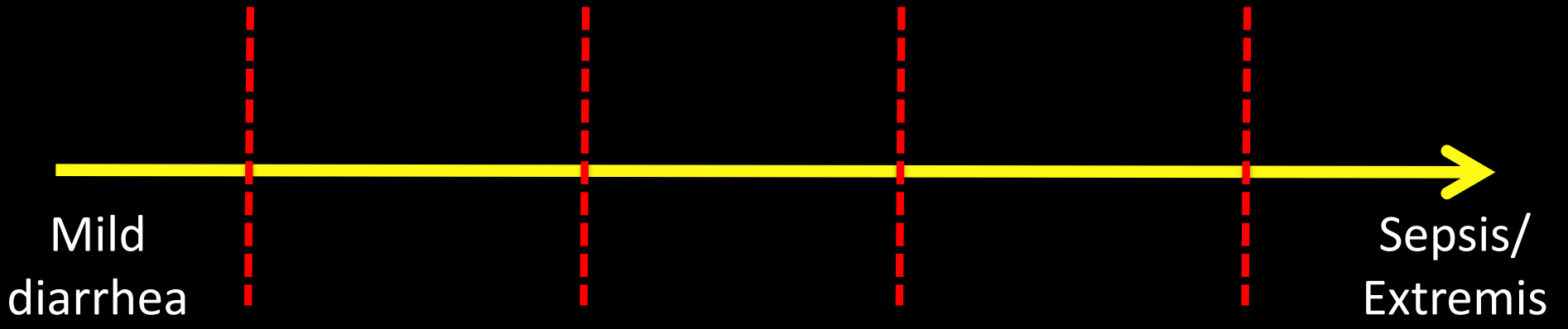


Severity Scoring and Treatment

Mild diarrhea

Sepsis/ Extremis

Severity Scoring and Treatment



Severity Scoring and Treatment

Severity	Criteria
Mild or Moderate:	WBC of 15K or lower *&* Serum creatinine <1.5 times pre-morbid level
Severe:	WBC of 15K or higher *or* Serum creatinine >1.5 times the premorbid level
Severe, Complicated:	Hypotension or shock, ileus, megacolon

-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

Severity	Criteria
Mild:	Diarrhea
Moderate:	Diarrhea plus any additional signs or symptoms not meeting severe or complicated criteria
Severe:	Any two of the following: -WBC≥ 15000cells/mm^3 -Serum albumin <3 g/dL -Abdominal tenderness

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
- -Hypotension/shock requiring vasopressors
- -Need for intubation/mechanical ventilation
- -Ileus/distention
- -Mental status changes

Laboratory values:

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

CT scan findings:

- -Pancolitis/ascites

ACG Severity Scoring and Treatment

Severity	Criteria
Complicated:	Any one of the following: -Admission to ICU for CDI -Hypotension with or without required use of vasopressors -End organ failure (Mechanical ventilation, Renal failure, etc) -Mental status changes -Fever ≥38.5° -Ileus or significant abdominal distention/tender -WBC≥ 35,000 cells/mm^3 -Serum lactate levels greater than 2.2 mmol/Liter

ACG Severity Scoring and Treatment

Severity	Criteria	Treatment
Mild:	Diarrhea	Metronidazole 500 mg PO tid
Moderate:	Diarrhea plus any additional signs or symptoms not meeting severe or complicated criteria	
Severe:	Any two of the following: -WBC≥ 15000cells/mm^3 -Serum albumin <3 g/dL -Abdominal tenderness	Vancomycin 125mg 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 vanco 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

The NEW ENGLAND JOURNAL of MEDICINE

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ORIGINAL ARTICLE

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

N Engl J Med 2011; 364:422-431 | February 3, 2011 | DOI: 10.1056/NEJMoa0910812

-Non-inferior to vancomycin for cure rate

-Lower recurrence rate compared to vanco

Novel medical treatment strategies for *Clostridium difficile infection*

Antibiotics:

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-Anti-Clostridium difficile toxin antibodies

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Biotherapy:

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-Non-toxigenic Clostridium difficile strains

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ORIGINAL ARTICLE

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.

N Engl J Med 2013; 368:407-415 | January 31, 2013 | DOI: 10.1056/NEJMoa1205037

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N Engl J Med 2013; 368:407-415 | January 31, 2013 | DOI: 10.1056/NEJMoa1205037

Hot Topics: Health Data Connected Care

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

Rebiotix®
Microbiota Restoration Therapy

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

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Recommended for recurrent disease

1st Recurrence: Vancomycin

2nd Recurrence: Vancomycin 7 week taper

3rd Recurrence: Fecal Microbiota Therapy

Severity Scoring and Treatment

Severity	Criteria	Treatment
Complicated:	Any one of the following: -Admission to ICU for CDI -Hypotension with or without required use of vasopressors -End organ failure (Mechanical ventilation, Renal failure, etc) -Mental status changes -Fever ≥38.5° -Ileus or significant abdominal distention/tender -WBC≥ 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**

Severity Scoring and Treatment

Role for Surgical Treatment?

but no controlled trials have been performed.

Colectomy can be life-saving for selected patients.[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.[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.[208]

Treatment of recurrent CDI. The frequency of further

-SHEA and IDSA Clinical Practice Guidelines 2010

Surgery and CDAD

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 MANAGAMENT AS SALVAGE THERAPIES!!!


COUNT 12

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

1: Arch Surg. 1992 Jul;127(7):847-52; discussion 852-3.

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]

ANNALS OF SURGERY
Vol. 235, No. 3, 363–372

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

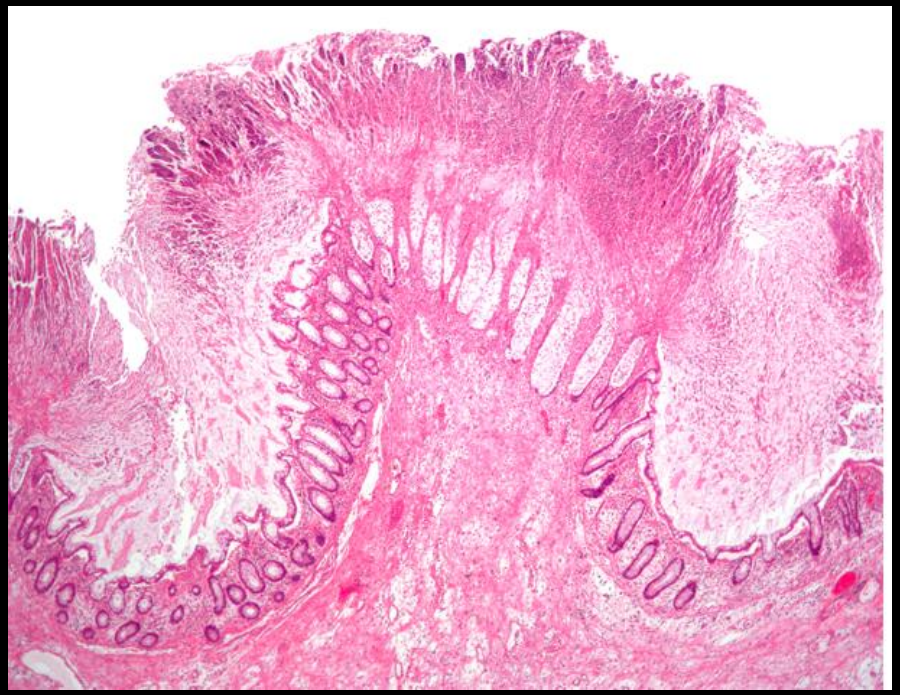
Is colectomy necessary for the treatment of severe, complicated (fulminant) CDAD?

Can we offer a procedure that adequately treats severe, complicated CDAD that is less morbid?

Pathophysiology

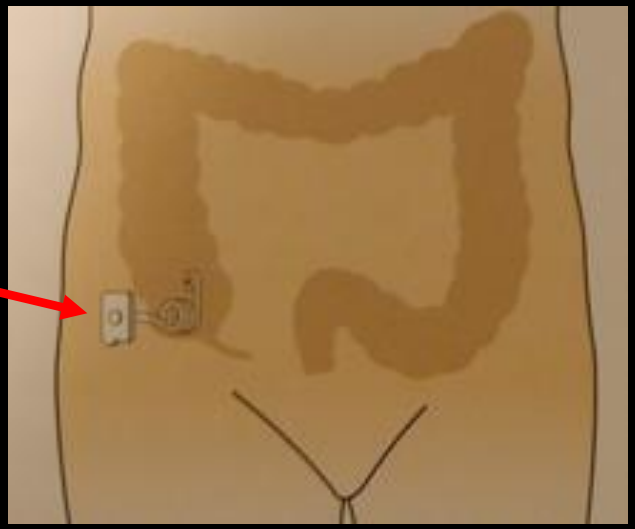
-*C. difficile* overgrows and produces exotoxins

-Toxins cause mucosal damage and inflammatory cell infiltration.



Hypothesis: Therapy to decrease bacterial counts and toxin levels throughout the whole colon will adequately treat severe, complicated CDAD.

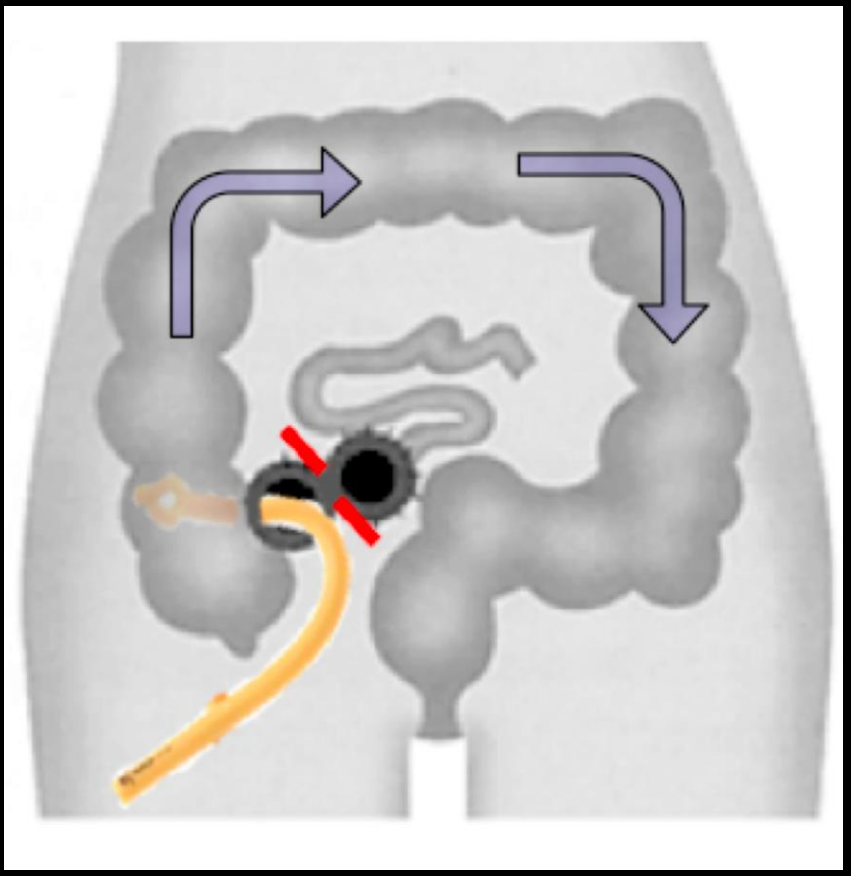
vancomycin



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

Ann Surg. 2011;254:423-429

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

	Ileostomy/washout	colectomy
APACHE-II (mean±S.D.)	31.4±9.0	29.9±8.9
Post-Operative Death	16/81* (20%)	40/81 (49%)

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

	Ileostomy/washout	colectomy
APACHE-II (mean±S.D.)	31.4±9.0	29.9±8.9
Post-Operative Death	16/81* (20%)	40/81 (49%)
Colectomy	5/81* (6%)	

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

	Ileostomy/washout	colectomy
Alive at 1 year	54/65 (83%)	30/41(73%)
Restoration of GI continuity	46/54 (85%)	7/30 (23%)

-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*.

	Ileostomy/washout	colectomy
APACHE-II (mean±S.D.)	31.4±9.0	29.9±8.9

?

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

	Ileostomy/washout	colectomy
APACHE-II (mean±S.D.)	31.4±9.0	29.9±8.9
Time from presentation to surgical consultation	11±9 hours	32±12 hours
Time from surgical consultation to operative intervention	9±6 hours	29±12 hours

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 of 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 of with TAC?
-Who is not a candidate for this operation?

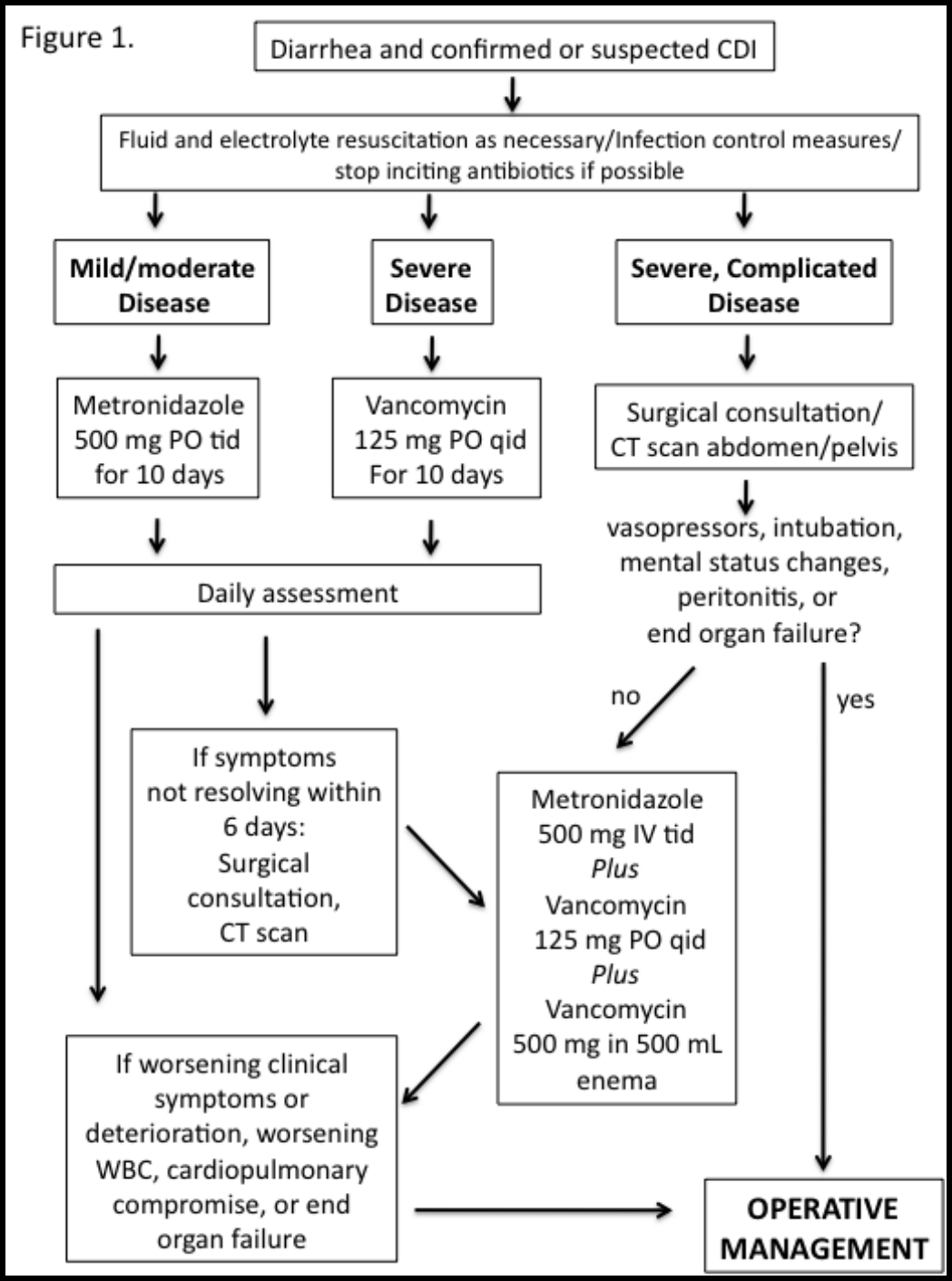
*Patients with colonic compromise.
*Abdominal compartment syndrome.

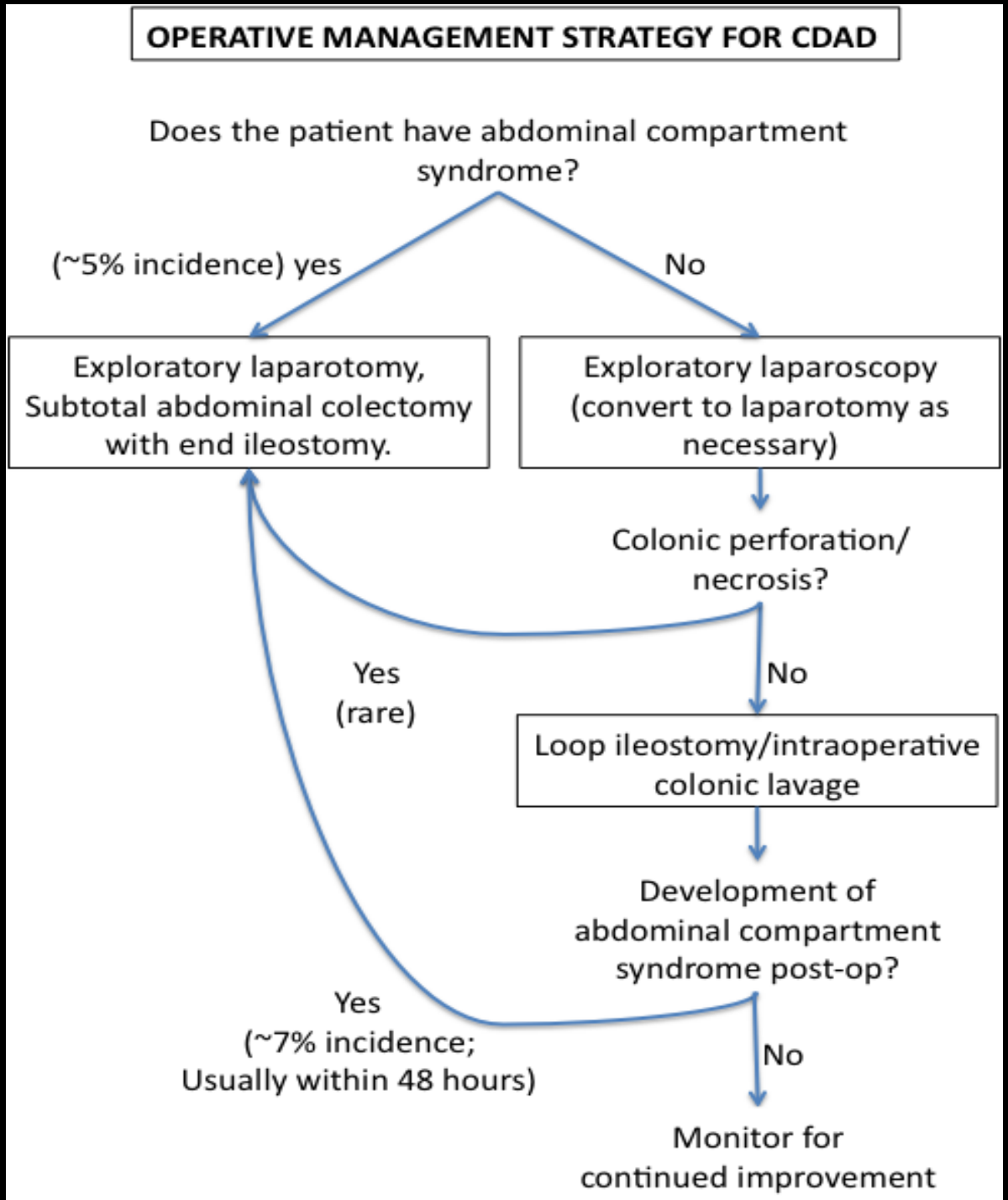
Loop ileostomy/colonic lavage v. total abdominal colectomy

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

*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
Severe Disease
Severe, Complicated Disease
Metronidazole 500 mg PO tid for 10 days
Vancomycin 125 mg PO qid For 10 days
Surgical consultation/ CT scan abdomen/pelvis
vasopressors, intubation, mental status changes, peritonitis, or end organ failure?
Daily assessment
no
yes
If symptoms not resolving within 6 days: Surgical consultation, CT scan
Metronidazole 500 mg IV tid Plus Vancomycin 125 mg PO qid Plus Vancomycin 500 mg in 500 mL enema
If worsening clinical symptoms or deterioration, worsening WBC, cardiopulmonary compromise, or end organ failure
OPERATIVE MANAGEMENT


OPERATIVE MANAGEMENT STRATEGY FOR CDAD
Does the patient have abdominal compartment syndrome?
(~5% incidence) yes
No
Exploratory laparotomy, Subtotal abdominal colectomy with end ileostomy.
Exploratory laparoscopy (convert to laparotomy as necessary)
Colonic perforation/ necrosis?
Yes (rare)
No
Loop ileostomy/intraoperative colonic lavage
Development of abdominal compartment syndrome post-op?
Yes (~7% incidence; Usually within 48 hours)
No
Monitor for continued improvement