10:45 – 11:45 am

New Approaches to Treating C Difficile Infection

SPEAKER
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Presenter Disclosure Information

The following relationships exist related to this presentation:

- Kalpana Gupta, MD, MPH: Consultant for Boehringer Ingelheim Pharmaceuticals, Inc. and Melinta Therapeutics. She and her spouse own stock in Antares Pharma, Inc.; Novartis Pharmaceuticals Corporation; Sarepta Therapeutics, Inc.; and Seattle Genetics Inc. Spouse is employed by Novartis Pharmaceuticals Corporation.

Off-Label/Investigational Discussion

- In accordance with pmiCME policy, faculty have been asked to disclose discussion of unlabeled or unapproved use(s) of drugs or devices during the course of their presentations.

New approaches to treating *Clostridium difficile* Infection

Kalpana Gupta

New Treatment Approaches to *Clostridium Difficile* Infection

Learning Objectives

- Distinguish risk factors for *C. difficile* infection (CDI) in an outpatient with recent diarrheal symptoms
- Consider the pros and cons of treatment modalities
- Employ prevention measures for clinicians, patients, and households

Case 1: Mr. Murray 70-Year-Old Man

Presents with:

- 4-6 loose stools/day
- Slight fever (100° F) x 5 days
- No unusual physical findings except for mild abdominal pain
- Denies nausea/vomiting, blood in stool, unusual diet or travel in recent weeks

Relevant PMH:

- COPD x 10 years, uses inhaler as needed
- GERD, for which he takes daily proton pump inhibitor (PPI)
- AECB 1-2 times per year
  - Last episode 6 weeks ago, for which he took a 10-day course of cefaclor

Urgent Threats:

1. *Clostridium difficile*
2. Carbapenem-resistant Enterobacteriaceae
3. Drug-resistant *Neisseria gonorrhoeae*

Centers for Disease Control and Prevention (CDC). Antibiotic resistance threats in the United States, 2013. Atlanta: CDC; 2013. http://www.cdc.gov/drugresistance/threat-report-2013/pdf/ar-threats-2013-508.pdf

C. difficile Infection (CDI)

- Although *C. difficile* is common in the environment, only 1 - 4% of adults are carriers
- Normal colonic microflora confers colonization resistance against *C. difficile*

Traditional risk factors:

- Age >65 years and/or underlying illness (weakened immune system)
- Recent antibiotic exposure (up to 3 months prior), resulting in disturbed colonic microflora (dysbiosis)
- Recent exposure to health care settings (hospital, long-term care facility, nursing home)

Bartlett JG and Perl TM. *N Engl J Med.* 2002;353:2503-2505.
Kujper J and van Dissel JT. *CMAJ.* 2008;179:747-748.
Bouza E et al. *Med Clin N Am.* 2006;90:1141-1163.

Traditional CDI Risk Factors (cont'd)

Other factors that disturb colonic microflora can put patients at risk:

- Bowel prep for colonoscopy or surgery
- Cytotoxic chemotherapy
- Colitis caused by IBD

Kelly CP. *JAMA.* 2009;301:954-962.

New Strain: BI/NAP1

- Since 2001, severe outbreaks have occurred in health care facilities in the U.S., Canada, and Europe.
- New Strain: North American pulsed-field gel electrophoresis Type 1 (NAP1)
- NAP1 strain testing is not FDA approved yet

NAP1 More Virulent		NAP1 More Resistant
Genetic variations enable it to produce:	**Result:**	**Particularly to fluoroquinolones:**
Greater quantities (at faster rates) of toxins A (16X) and B (25X)	"Hypervirulent"	Wide fluoroquinolone use in recent years has contributed to NAP1 emergence

McDonald LC, et al. *N Engl J Med.* 2005;353:2433-2441.
Pepin J, et al. *CMAJ.* 2005;173(9):1037-1042.
Sunenshine RH, McDonald LC. *Cleve Clin J Med.* 2006;73:187-197.

Community-Acquired CDI: A New Disease Entity

Less than 1/5 of all disease appears to be community-associated

Population-based study in the UK

50% of elderly patients diagnosed with CDI had no history of antibiotic exposure in the 45 days prior to being admitted to hospital for CDI.

North Carolina County Study

- 25/100,000 overall incidence of community-associated CDI
- Women at higher risk than men
- Within the preceding 3 months:
  - 59% had no exposure to antibiotics
  - 23% had taken a proton pump inhibitor (PPI)
  - Only 59% had visited a facility as outpatients

Kujper J and van Dissel JT. *CMAJ.* 2008;179:747-748.
Dial S, et al. *CMAJ.* 2008;179:767-72.

Community-Associated C. *difficile* *Connecticut 2006*

Clinical features among patients with community-associated *C. difficile*

Characteristic	#	%
Abdominal Pain (n=222)	169	(76)
Vomiting (n=221)	50	(23)
Diarrhea (n=236)	227	(96)
Bloody diarrhea (n=209)	48	(23)
Fever (n=203)	56	(28)

Adapted from Rabatsky-Ehr T, et al. *MMWR.* 2008; 57(13):340-343.

CDI Risk Factors: A Closer Look at PPIs

Increasing evidence identifies PPI exposure as an independent risk factor for community-associated CDI

- Adjusted RR = 2.9 (95% CI, 2.4-3.4) in Canadian general practice database

Vegetative form of *C. difficile* has been shown to survive in gastric contents with a raised pH

- Could shorten time needed for ingested acid-resistant spores to change to vegetative cells

RR = relative risk

Jump RLP, et al. *Antimicrob Agents Chemother.* 2007;51:2883-2887.
Dial S, et al. *JAMA.* 2005;294:2989-2995.

Possible New Modes of Transmission?

Reports of C. difficile in food:

- Retail meat in Canada (2007)[1]
- Retail meat (both uncooked and ready-to-eat) from supermarkets in Tucson, AZ (2007)[2]
  - Including about a quarter identified as NAP1 or NAP1-related strains*
  - All isolates were positive for toxins A and B, and binary toxin
- Ready-to-eat (imported) salads in Glasgow, Scotland (2008)[3]

[1] Rodriguez-Palacios A, et al. *Emerg Infect Dis.* 2009;15:802-805.
[2] Songer JG, et al. *Emerg Infect Dis.* 2009;15:819-821.
[3] Bakri MM, et al. *Emerg Infect Dis.* 2009;15:817-818.

*NAP1 strain testing is not FDA approved yet.

Testing for CDI

- Absence of traditional risk factors no longer rules out CDI
- Testing is merited even in patients who have no known risk factor
- Only diarrheal stools should be tested (unless intestinal ileus is present)

Kujper J et al. *CMAJ.* 2008;179:747-748.
Sunenshine RH et al. *Cleve Clinic J Med.* 2006;23:187-197.

Testing for *C. difficile* Infection

Test	Description	Sensitivity	Specificity	Speed of Reports
EIA (enzyme immunoassay)	Detects toxin A or toxins A plus B	70-80%	>97%	Hours
GDH (glutamate dehydrogenase)	Detects a common antigen, not a toxin, of *C. difficile*; immunoassay is preferred over latex agglutination	70-80%	<90%	Hours
qPCR (qualitative real-time polymerase chain reaction)	Detects Toxin B or toxin regulator genes; commercial and locally developed tests are available	>90%	>97%	Hours
Anaerobic culture for toxigenic C. *Difficile*	Detects Toxin B	>90%	95-97%	2 to >3 d
Direct stool cytotoxin with tissue culture	Detects Toxin B	70-80%	>97%	2 to >3 d

Adapted from Peterson LR et al. *Ann Intern Med.* 2009;151:176-179.

C. difficile – Diagnosis Summary

- In patients with new diarrhea, *C. difficile* infection should be in the differential diagnosis
  - Increased risk if antibiotic or health care exposure
- *C. difficile* spores can be carried in the gut
  - Asymptomatic patients should not be tested and do not warrant therapy
- Test stool only in actively symptomatic patients
  - PCR is best test (highly sensitive)
  - EIA less sensitive; if high clinical suspicion, start empiric therapy even if this test is negative, and send a PCR

MMWR / August 10, 2012 / Vol. 61 / No. 31

Sniff Test?

C. difficile produces a unique odor attributed to a phenol: p. cresol

A dog's olfactory sense is 300X that of humans

Bomers MK et al. BMJ 2012;345:e7396 doi: 10.1136/bmj.e7396

C. difficile Infection: Signs and Symptoms

Asymptomatic

Host develops no symptoms, but remains a potential carrier.

Mild

- Mild to moderate non-bloody diarrhea
- Mild abdominal cramps
- +/- low-grade fever

Severe

- Profuse watery diarrhea
- Fever, nausea, dehydration often occur
- Pseudomembranous colitis OR any 2 of these features:
  - Age >60 years
  - Temp >101°F
  - Serum albumin <2.5 mg/dL
  - Peripheral white blood cell count >15,000 uL

Adapted from Kelly CP. *JAMA.* 2009;301(9):954-962.
Sunenshine RH, McDonald LC. *Cleve Clin J Med. 2006;73:187-197.*

SHEA/IDSA Clinical Practice Guidelines

- Mild or moderate CDI
  - Peripheral WBC of ≤ 15,000/μL and serum creatinine <1.5 times the baseline
- Severe CDI
  - Peripheral WBC of > 15,000/μL or a serum creatinine >1.5 times the baseline
- Severe, complicated CDI
  - Shock, ileus, megacolon; hypotension

SHEA =Society for Healthcare Epidemiology of America
IDSA =Infectious Diseases Society of America

Cohen SH et al. Infect Control Hosp Epidemiol 2010; 31(5): 431-455.

Complications of Severe CDI

- Mild disease can quickly progress to moderate or severe disease.
- Serious, potentially life-threatening complications:
  - Pseudomembranous colitis
  - Paralytic Ileus
  - Toxic megacolon
  - Intestinal perforation
  - Sepsis
- Overall, attributable mortality rate for CDI: 6–15%
- After surgery for complications of CDI, mortality rate rises to 32–50%.

Findings that appear predictive of more serious complications:

Increased creatinine

High white blood cell count

High lactate level

Sunenshine RH et al. *Cleve Clinic J Med.* 2006;23:187-197.
Bartlett JG, et al. *Clin Infect Dis.* 2008; 46:S3-49.

C. difficile – Treatment Principles

Stop other antibiotics, if possible*

Avoid antimotility agents

Supportive Care
- Fluids
- Diet as tolerated

Initiate CDI Therapy
- If diarrhea (or abdominal pain/distension if ileus) and a positive test
- Not just for a positive test in absence of GI symptoms
- Empiric treatment OK if strong clinical suspicion

* Concomitant antibiotics prolong diarrhea and increase risk of recurrence

Mullane KM, et al. *Clin Infect Dis.* 2011;53(5):440-447.
Hu MY, et al. *Gastroenterology.* 2009;136(4):1206-1214.

SHEA/IDSA Clinical Practice Guidelines for Initial Episode of CDI

- Mild or moderate CDI (A-I)
  - Peripheral WBC of ≤ 15,000/μL and serum creatinine <1.5 times the baseline
    - Metronidazole, 500 mg orally 3 times daily X 10-14 d
- Severe CDI (B-I)
  - Peripheral WBC of > 15,000/μL or a serum creatinine >1.5 times the baseline
    - Vancomycin, 125 mg orally 4 times daily X 10-14 d
- Severe, complicated CDI (C-III)
  - Shock, ileus, megacolon; hypotension
    - Vancomycin (orally or NG tube), 500 mg 4 times daily AND metronidazole, 500 mg intravenously every 8 hours
      - » Vancomycin by rectum when ileus present

Cohen SH et al. Infect Control Hosp Epidemiol 2010; 31(5): 431-455.

Antimicrobials for CDI

	Metronidazole	Vancomycin	Fidaxomicin
Approved by FDA for CDI	No, but efficacy supported by early RCTS; equals that of vancomycin[1,2,3]	Yes	Yes
Comparative Cost	$	$$	$$$$
Form used for CDI	Oral IV for severe or complicated disease	Oral, intragastric or enema	Oral
Duration	10-14 days	10-14 days	10-14 days
Notes	Preferred for mild to moderate disease	Preferred and more effective for severe disease; Also indicated when metronidazole cannot be used or is not effective.	Equal efficacy to vancomycin but may have lower recurrence rates Nausea (11%) Vomiting (7%) Abdominal pain (6%)

Khanna S, et al. Mayo Clin Proc. 2012;87(11):1106-1117.; Louie TJ, et al. *N Engl J Med.* 2011;364(5):422-431 Fidaxomicin Prescribing Information: http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/201699s000lbl.pdf

Case 2: Mr Conti

- 60-year-old man with COPD and diabetes
- Hospitalized for a COPD exacerbation 2 weeks ago
- Presents for post-hospitalization follow-up
- His COPD is stable
- Was told he had *C. difficile* while in the hospital and finished his course of oral metronidazole* last week
- Reports that he has no more diarrhea

*Metronidazole is not FDA-approved for treatment of CDI.

Recurrent CDI

Up to 30% of patients with CDI have recurrence within 3 months

- Increased risk if antibiotic or proton pump inhibitors

If relapse of diarrhea in patient with recent CDI… ⇨	test for CDI recurrence
Empiric treatment if… ⇨	fever, distended abdomen, high white blood cell count and high clinical suspicion

Linsky A, et al. *Arch Intern Med.* 2010;170(9):772-778.
Khanna S, Pardi DS. *Mayo Clin Proc.* 2012;87(11):1106-1117.

SHEA/IDSA Clinical Practice Guidelines

First recurrence treated same as initial episode

- Mild or moderate CDI (A-I)
  - Peripheral WBC of ≤ 15,000/μL and serum creatinine <1.5 times the baseline
    - Metronidazole, 500 mg orally 3 times daily X 10-14 d
- Severe CDI (B-I)
  - Peripheral WBC of > 15,000/μL or a serum creatinine >1.5 times the baseline
    - Vancomycin, 125 mg orally 4 times daily X 10-14 d
- Severe, complicated CDI (C-III)
  - Shock, ileus, megacolon; hypotension
    - Vancomycin (orally or NG tube), 500 mg 4 times daily AND metronidazole, 500 mg intravenously every 8 hours
      - » Vancomycin by rectum when ileus present

Cohen SH et al. Infect Control Hosp Epidemiol 2010; 31(5): 431-455.

Recurrent CDI Treatment

Second recurrence
• Oral vancomycin tapered over 6 wk
✓ 125 mg 4 times daily for 14 d
✓ 125 mg 2 times daily for 7 d
✓ 125 mg once daily for 7 d
✓ 125 mg once every other day for 8 d
✓ 125 mg once every 3 d for 15 d

Khanna S, et al. *Mayo Clin Proc.* November 2012;87(11):1106-1117.

Additional Recurrent CDI Treatment Options

Future Additional Recurrences

- Oral vancomycin, 125 mg 4 times a day for 14 days, followed by rifaximin, 400 mg twice daily for 14 days
- Consider combination therapy with oral vancomycin and oral rifaximin
- Consider intravenous immunoglobulin, 400 mg/kg, repeated up to 3 times at 3-week intervals
- Consider fecal microbiota transplantation

Khanna S, Pardi DS. *Mayo Clin Proc.* 2012;87(11):1106-1117.

Fecal Microbiota Transplantation

- First described in 1958
- Reluctance to accept?
  - Aesthetically unappealing
  - Logistically challenging
  - Lack of efficacy data from randomized, controlled trials

Kelly CP. N Engl J Med. 2013 Jan 31;368(5):474-

Fecal Microbiota Transplantation (FMT)

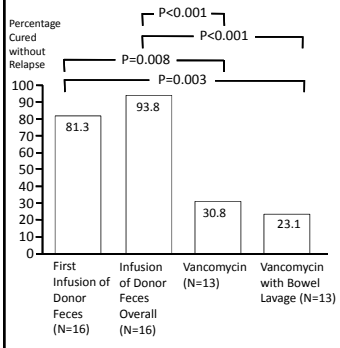

Figure 2. Rates of Cure without Relapse for Recurrent Clostridium difficile Infection

van Nood E et al. N Engl J Med 2013; 368:407-415

Fecal Microbiota Transplant: Overview

Evidence	Multiple observational and randomized studies showing benefit • Resolution of diarrhea and associated symptoms within 24 hours to 12 days • Donor fecal microbiota remains stable over a 24-week period
Formulations	• Slurry • Pills (RCT preliminary findings at ID Week 2013)[1]
Routes	Upper GI • Lower GI (enema vs. colonoscope) • NGT
Who	Patients with severe and recurrent CDI who have failed multiple attempts at conventional antibiotic
Where	Center of expertise
Risks	• Those associated with NGTs and colonoscopy • Potential of transmission of infectious agents contained in the stool

1. Louie T, et al. Abstract #89. Infectious Disease Week, San Francisco, CA, Oct 206, 2013.

Fecal Microbiota Transplant: How It's Done

Screening

Screen Donor

Serum: CBC, hepatitis A, B, and C; HIV-1 and HIV-2, syphilis
Stool: fecal Giardia antigen, cryptosporidium antigen, acid fast stain for Cyclospora, Isospora, and H. pylori fecal antigen; enteric bacterial pathogens ; O&P; Cdiff
Clinical: no ABX past 3 months, no IBD; clinically well

Screen Recipient

hepatitis A and B; HIV-1

Kelly CR et al. J Clin Gastroenterol. 2012 Feb;46(2):145-9.. Mattia E et al. Gastroenterology. 2012;142(3):490. Hamilton MJ et al. Am J Gastroenterol. 2012;107(5):761.

Fecal Microbiota Transplant: How It's Done

Treatment

Oral vancomycin: 500mg BID x 7 days then…

3–4 liters of polyethylene glycol lavage

200–300 g of donor stool in 200–300 mL of sterile normal saline (homogenize in blender to a liquid consistency)
Administer via enema within 10 minutes of preparation
Retain the enema for at least 6 hours
Repeat daily for 5 days

OR a single infusion of 200–300 g of stool suspension into colon (but risk of perforation)

Kelly CR et al. J Clin Gastroenterol. 2012 Feb;46(2):145-9.. Mattia E et al. Gastroenterology. 2012;142(3):490. Hamilton MJ et al. Am J Gastroenterol. 2012;107(5):761.

Fecal Microbiota Transplant (FMT): How to Get It Done

- Current US FDA Regulations only allow FMT for treatment of *C. difficile* infection that does not respond to standard treatment, unless part of an approved clinical trial

Fecal Transplant- Mail Order

http://www.openbiome.org/

- Nonprofit 501(c)(3) organization; MIT/Harvard faculty
- Provides material that is concentrated and packaged for either colonoscopic or nasogastric administration
- $250 per unit of stool
- service fee of $250 per treatment to recover the costs of donor screening, lab management, and material preparation
- CPT code 44705, *Preparation of fecal microbiota for instillation, including assessment of donor specimen*
- Orders are processed and delivered within 5 business days
  - Need to keep frozen
- Current FDA guidance allows use for CDI

But new draft regulation may restrict use to stool that is collected and screened by the treating physician

Stool Substitute Transplant Therapy for the Eradication of *Clostridium Difficile* Infection: 'Repoopulating' the Gut

- *"Here we report the successful outcome of two patients with recurrent CDI unresponsive to conventional therapy who received a stool substitute, a preparation of 33 different intestinal bacteria isolated in pure culture, from a single healthy donor.."*
- Report of 2 patients with recurrent C. difficile infection (strain riboype 078) who were successfully treated with RePOOPulate synthetic stool preparation
  - Both patients remained without symptoms at 6 months post-treatment

Petrof EO et al. Microbiome 2013, 1:3

Prevention of CDI

- Handwashing!
- Prudent use of antimicrobials
- Addition of probiotics containing viable lactobacilli or *Saccharomyces* species to antibiotic regimen
  - Cuts incidence of antibiotic-associated diarrhea in half
  - More studies needed to confirm its ability to protect against CDI

Kelly C. *JAMA*. 2009;301:954-962.
McDonald LC, et al. *N Eng J Med*. 2005; 353:2433-2441.

Which Antibiotics are High Risk?

- Despite recent trends, antimicrobial therapy is still the most important risk factor for CDI.[1]
- Studies conflict when determining agent at highest risk, as many antimicrobials have been linked to increased CDI risk.
- Historically, cephalosporins and clindamycin were associated with highest risk, as well as ampicillin/ amoxicillin.[2]
- Use of multiple antibiotics over longer periods elevates risk.[3]

[1] Kelly CP and LaMont TJ. *N Engl J M ed*. 2009;360:637.
[2] Muto CA, et al. *Infect Control Hosp Epidemiol*. 2005;26:273-280.
[3] Bignardi GE. *J Hosp Infect* .1998;40:1-15.

Which Antibiotics Are High Risk, Given Changing Epidemiology?

Large recent study of community-based population using Canadian health databases

Adjusted relative risk of developing CDI within 45 days of using any antibiotic was 10.6.

Risk of individual agents:

Agent	Adjusted RR (95% CI)
Clindamycin	31.8 (17.6-57.6)
Gatifloxacin	16.7 (8.3-33.6)
Cephalosporins	14.9 (10.9-20.3)
Moxifloxacin	9.1 (4.9-17.0)
Ciprofloxacin	5.0 (3.7-6.9)
Penicillins	4.3 (2.8-6.4)
Levofloxacin	4.1 (2.4-7.1)
Macrolides	3.9 (2.5-5.9)

Dial S, et al. *CMAJ*. 2008;179 :767-772.

C. Difficile Prevention through Antimicrobial Stewardship

Antibiotic Stewardship

- Avoid empirical use of broad-spectrum antibiotics

"High Risk" antibiotics for *C. difficile* include:

- 3rd generation cephalosporins, fluoroquinolones, and clindamycin

"Lower Risk" antibiotics

- Aminoglycosides, macrolides, sulfonamides, tetracyclines

C. difficile Prevention: Probiotics

Formulations of live bacteria and fungi that act by maintaining bowel flora and prevent colonization of pathogens

- *Bifidobacterium* spp., *Saccharomyces* spp., *Lactobacilli* spp
- Larger doses are more effective (>10 billion CFU/day)
- Many formulations available OTC in health food stores

Johnston BC, et al. *Ann Intern Med*. 2012;157:878-888.
Goldenberg JZ, et al. *Cochrane Database Syst Rev*. 2013;CD006095.
Allen SJ, et al. Lancet. 2013;382(9900):1249-1257.
Surawicz CM, et al. *Am J Gastroenterol*. 2013;108(4):478-498.

C. difficile Prevention: Probiotics

Conflicting evidence:

- 20 RCTs of probiotics showed[1]
  - 66% reduced risk (RR 0.34 [0.24;0.49]) in *C. difficile*-associated diarrhea (CDAD) in patients receiving antibiotics
  - No difference in adverse event rates from control groups
- Insufficient evidence to support use of probiotics to prevent CDI[4]
- Probiotics did not prevent antibiotic or CDAD in hospitalized patients ≥ 65 getting antibiotics[3]
- Probiotics reduced CDAD and antibiotic associated diarrhea (AAD) in patients receiving antibiotics[2]
- The benefit of probiotics for prevention of CDAD is uncertain

Johnston BC, et al. *Ann Intern Med*. 2012;157:878-888.
Goldenberg JZ, et al. *Cochrane Database Syst Rev*. 2013;CD006095.
Allen SJ, et al. Lancet. 2013;382(9900):1249-1257.
Surawicz CM, et al. *Am J Gastroenterol*. 2013;108(4):478-498.

C. difficile Prevention: Probiotics

Give probiotic 2 hours separated from oral antibiotic dose

- Continue probiotics for 3-14 days after end of antibiotic therapy

Risks of probiotic associated infection are minimal

- Rare cases of bacteremia and fungemia
- Avoid probiotics in patients with immune compromise, endocarditis risk, recent GI or heart surgery, acute pancreatitis, diseases that compromise GI barrier function

Goldenberg JZ, et al. Cochrane Summaries. May 2013. http://summaries.cochrane.org/CD006095/the-use-of-probiotics-to-prevent-c.-difficile-diarrhea-associated-with-antibiotic-use

CDI Prevention and Precautions

For Clinicians

- Hand Hygiene! Clean hands with soap and water (preferred) or alcohol based rub before and after caring for every patient *
- Contact precautions (gowns/gloves)
- Environmental disinfection (bleach)
- Limit antibiotics

For Patients

- Hand Hygiene! (yourself and your provider)
- Only use antibiotics when prescribed

For Households

- Hand Hygiene! (yourself and your family)
- Keep high touch surfaces clean

* Alcohol does not effectively kill *C. difficile* spores

CDC. FAQs about Clostridium Difficile. http://www.cdc.gov/HAI/pdfs/cdiff/Cdif_largertext.pdf

CDI: Take-Home Points

- New, more virulent disease strains have made timely diagnosis and treatment more critical:
  - Diarrhea accompanied by fever or lasting >3 days or should be evaluated and treated
  - Consider CDI in all pts with persistent severe diarrhea, even if traditional risk factors are absent or in the distant past
  - Marked leukocytosis suggests more serious disease
- Patients with confirmed or potential CDI should be vigilantly monitored daily, as rapid deterioration can occur
- Contact precautions, hand hygiene and environmental disinfection important for prevention/control
- Prescribe antibiotics prudently