Goal. The goal of this lesson is to provide a review of Clostridium difficile infection (CDI) to include epidemiology and pathophysiology of the disease, risk factors, transmission, clinical diagnosis, and adult treatment. In addition, a new entity and treatment option for CDI, fidaxomicin (Dificid®), will be reviewed. Surgical and non-pharmacological treatment will not be discussed in this lesson.

Objectives. At the completion of this activity, the participant will be able to:
1. demonstrate an understanding of the epidemiology, pathophysiology, risk factors, transmission, and clinical diagnosis for CDI;
2. recognize the general treatment options and management of CDI; and
3. identify key prescribing and counseling points for each entity discussed including fidaxomicin (Dificid®).

Introduction
Clostridium difficile (C. difficile) is an obligate anaerobic, spore-producing, gram positive rod that was first described in 1935. It has since been linked with Clostridium difficile-associated diarrhea (CDAD) and pseudomembranous colitis, an infection of the large intestine characterized by an inflamed and bleeding lining of the colon. C. difficile is the responsible pathogen in 20 to 30 percent of patients with antibiotic-associated diarrhea, 50 to 75 percent of those with antibiotic-associated colitis, and more than 90 percent of those with antibiotic-associated pseudomembranous colitis. Additional complications may include bowel perforation and septicemia resulting in death. CDI or CDAD was traditionally considered a hospital-acquired infection affecting elderly and frail patients, but is now presenting in the community setting. The rates of CDI are increasing dramatically, and some experts feel it is an under-recognized cause of severe illness and death. CDI is an important public health concern which demands additional media and public health awareness and prevention education.

Epidemiology
According to a study published by the Centers for Disease Control and Prevention (CDC) in 2007, reported mortality rates from C. difficile disease in the United States increased from 5.7 per million population in 1999, to 23.7 per million in 2004. The study also found that mortality rates were higher for whites than for other racial or ethnic groups. One reasonable justification for this observation may be attributed to racial/ethnic differences in insurance status and access to care. Whites are more likely to receive antimicrobial treatment putting them at risk for CDI. It is also hypothesized that the increased rate of overall mortality may be due to the emergence of highly virulent strains of C. difficile such as the North American pulsed-field type 1 (NAP1), restriction-endonuclease analysis type BI, and polymerase chain reaction (PCR) ribotype 027, collectively referred to as the NAP1/BI/027 strain. This virulent strain is also associated with the production of 10 times more toxin A, up to 23 times more toxin B, and a third toxin referred to as binary toxin. In addition, it is resistant to fluoroquinolones which may have contributed to its prevalence. Since the emergence of the NAP1/BI/027 strain, CDI is now being diagnosed in the community and is affecting patients previously considered low risk for contracting the disease, including young, healthy individuals without prior exposure to hospitals or antibiotics.

Pathogenesis
The pathogenesis of CDI requires a three-step process (Figure 1). First, an alteration of the normal colonic microflora by antibiotics occurs or, rarely, from chemotherapeutic agents. Clindamycin was the first antibiotic to be associated with pseudomembranous colitis; however since then almost all antimicrobials have been linked with CDAD. There also appears to be a relationship between the widespread use of fluoroquinolones and CDAD. Table 1 lists the frequency for which antimicrobials are associated with CDAD and colitis. Cancer chemotherapy agents that possess antimicrobial properties and bowel preparation regimens rarely result
Antimicrobial agents that predispose to Clostridium difficile-associated diarrhea and colitis

<table>
<thead>
<tr>
<th>Most Frequently</th>
<th>Ampicillin and amoxicillin</th>
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<tr>
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<td>Cephalosporins</td>
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<td></td>
<td>Clindamycin</td>
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<td></td>
<td>Fluoroquinolones</td>
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<tr>
<td>Less Frequently</td>
<td>Macrolides (including erythromycin)</td>
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<td></td>
<td>Other penicillins</td>
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<td></td>
<td>Sulfonamides</td>
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<td></td>
<td>Trimethoprim/sulfamethoxazole</td>
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<td>Rarely or Never</td>
<td>Bacitracin</td>
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<td>Carbapenems</td>
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<td>Chloramphenicol</td>
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<td>Parenteral aminoglycosides</td>
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<td>Rifampin</td>
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<td>Tetracycline</td>
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<td>Tigecycline</td>
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<td>Vancomycin</td>
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Risk Factors
Risk factors for the development of CDI in addition to antimicrobial therapy include increasing age, severity of underlying disease, use of nasogastric tubes, gastrointestinal procedures, and length of hospital stay. Additionally, patients undergoing cytotoxic chemotherapy and those with human immunodeficiency virus (HIV) are also at risk due to frequent antibiotic usage, nosocomial exposure, and severe comorbidity.

In February 2012, the Food and Drug Administration (FDA) issued a drug safety communication regarding the possible association of CDAD and stomach acid drugs. While proton pump inhibitors (PPIs) are specifically highlighted in this drug safety communication, H2 antagonists are also being investigated. FDA states that patients taking PPIs who develop diarrhea that does not improve should be considered for a CDAD diagnosis. They are also working with manufacturers to update the PPI labels with the added cautionary statement regarding the increased risk of CDAD with PPI use. Because gastric acidity is a mechanism that protects the host against ingested pathogens, it is proposed that the reduction of gastric acid could allow a greater number of viable C. difficile spores to reach the colon. However, spores are considered to be relatively acid-resistant. Other experts suggest that there is an antibiotic effect with PPIs that changes the flora of the lower intestine. Past studies have been observational, and randomized trials are needed to determine the strength of the association.

Transmission
The primary mode of C. difficile transmission resulting in disease is person-to-person spread through the fecal-oral route, primarily within healthcare facilities (e.g., long term care, rehabilitation). The most important infection control measures include (1) the use of gloves and gowns by healthcare workers and visitors upon entry into the hospital room of a patient with CDI; (2) compliance with good hand hygiene; and (3) private hos-
pital rooms, where possible, with contact precautions for the duration of diarrhea. It is important to note that alcohol-based hand sanitizers which are commonly available in healthcare facilities are not effective in killing *C. difficile* in its spore form, and may just displace the spores. Spores should be removed by washing hands with soap or chlorhexidine and running water.

**Diagnosis**

The diagnosis of *C. difficile* diarrhea should be considered in any patient with acute diarrhea who has received antibiotics within the previous three months, and especially in anyone whose diarrhea began 72 hours or more after hospitalization. *Clostridium difficile* infection is defined by the presence of symptoms which is usually diarrhea (passage of three or more unformed stools in 24 or fewer consecutive hours), and either a positive stool test for *C. difficile* toxins or toxigenic *C. difficile*, or colonoscopic or histopathologic findings revealing pseudomembranous colitis. Testing for *C. difficile* or its toxins should only be performed on diarrheal (unformed) stool, unless ileus due to *C. difficile* is suspected. Ileus is a condition where the bowel is not working correctly, leading to an immobility issue where no structural problem exists. In patients with ileus or colonic distension with minimal or no diarrhea, testing can be done on available stool. Various methods are used to test stool for CDI. They differ in cost, speed of results, specificity, and sensitivity. The same criteria are used to diagnose recurrent CDI. Recent use of antibiotics is not required for diagnosis due to occasional reports of community-acquired cases.

**Treatment**

The first step in treating CDI is to discontinue therapy with the causative antimicrobial agent(s) as soon as possible in order to reduce the risk of recurrent infection. In 15 to 25 percent of patients, diarrhea may resolve without specific *C. difficile* treatment. However, this therapy alone is not recommended for patients who are severely ill or who have other medical problems. If severe or complicated CDI is suspected, empirical treatment should begin as soon as the diagnosis is suspected, followed by stool toxin assay for confirmation. If the result is negative, the decision to alter therapy must be individualized. Antiperistaltic agents, such as loperamide, should be avoided when possible as they may hide symptoms and precipitate toxic megacolon.

**Initial Episode of CDI**

According to the 2010 clinical practice guidelines published by the Society for Healthcare Epidemiology of America (SHEA) and the Infectious Diseases Society of America (IDSA), the following recommendations have been provided for CDI treatment in adults. Metronidazole is the drug of choice for an initial episode of mild to moderate CDI at a dosage of 500mg orally three times a day for 10 to 14 days. Vancomycin is the drug of choice for an initial episode of severe CDI at a dosage of 125mg orally four times a day for 10 to 14 days (some references suggest doses of 125-500mg for moderate to severe CDI while higher doses are generally reserved for more critical patients). Vancomycin orally (and per rectum, if ileus is present, since ileus may prevent the delivery of oral vancomycin to the colon) with or without intravenous metronidazole is the regimen of choice for the treatment of severe, complicated CDI. In this instance, the guidelines suggest vancomycin 500mg orally four times a day and 500mg in approximately 100mL normal saline per rectum every six hours as a retention enema. Metronidazole should be dosed at 500mg intravenously every eight hours. These agents will be discussed in further detail in this lesson.

**Recurrent CDI**

Recurrent CDI is either a result of a relapse of the infection due to the original strain, or re-infection of patients who remain susceptible and are exposed to a new strain. For the first recurrence, the same antibiotic that was used for the initial episode is recommended. However, vancomycin should be chosen over metronidazole if the white blood cell (WBC) count is 15,000 cells/µL (15) or higher, or if the patient has a rising serum creatinine (SCr) level indicating that the patient is at a higher risk of developing complications.

The recommended treatment for a second recurrence is vancomycin, using a tapered or pulse regimen. Metronidazole is not recommended beyond the first recurrence or for long term therapy because it may be associated with cumulative neurotoxicity. The following is an example of an acceptable taper schedule; however, there are various regimens. Begin with vancomycin 125mg orally four times a day for 10 to 14 days, followed by 125mg two times a day for one week, followed by 125mg once per day for a week, followed by 125mg every two or three days for two to eight weeks. The rationale behind this tapered regimen is that it allows time for the spores to convert to the *C. difficile* vegetative forms and then be killed on the days that vancomycin is administered. It also allows the *C. difficile* vegetative forms to be kept in balance while allowing the normal flora to be reestablished. While the taper/pulse course has shown efficacy, concern does exist that vancomycin will increase susceptibility to CDI by killing off too much of the gram positive organisms in the gut. It may also predispose the patient to vancomycin-resistant enterococci (VRE). *C. difficile* resistance to vancomycin is rare.

There are a number of other treatment options that may be attempted if further failure occurs. In addition to the select newer alternative antimicrobials that will be discussed below, evidence suggests that intravenous immunoglobulin infusion and fecal microbiota
transplantation are encouraging options. Toxin binders, such as cholestyramine and colestipol, may be used as adjunct therapy to control diarrhea, but should not be prescribed as primary therapy.

Select Antibiotics for the Treatment of CDI

Table 2 includes recommendations for the treatment of *Clostridium difficile* infection. **Metronidazole (Flagyl®).** Metronidazole is preferred as first line for mild to moderate disease because it is inexpensive and effective. Data prior to 2000 indicated that the failure rates for treatment with metronidazole and vancomycin were very similar. However, since 2000, higher failure rates have been reported with metronidazole (average 19 percent, ranging from 7 to 38 percent). In a retrospective study, the time to resolution of diarrhea in metronidazole-treated patients was significantly longer than in those treated with vancomycin. In mild disease, both treatments yield similar response rates, leading to the recommendation that metronidazole only be used first line for mild to moderate disease.

Oral metronidazole therapy is well absorbed in the upper intestine and reaches high fecal concentrations in patients with *C. difficile* colitis because it is secreted through inflamed intestinal mucosa. The tablet may also be crushed and administered through a nasogastric tube if needed. Intravenous metronidazole is an alternative for patients who can’t tolerate oral medication. Metronidazole is a pregnancy category risk factor B, yet contraindicated in the first trimester. It has been carcinogenic in some animal species raising concern that it should not be used during pregnancy. The American Academy of Pediatrics (AAP) rates metronidazole as not compatible with nursing, as it enters breast milk and is not recommended for long term therapy and during pregnancy. When given orally, it is a pregnancy risk factor B (injection is category C). It does enter breast milk and is not recommended for nursing mothers. It may be administered through a nasogastric tube if oral administration is not possible. In addition, oral, nasogastric, and rectally administered vancomycin are not systemically absorbed from the gut; therefore, systemic laboratory monitoring does not generally apply. However, in some cases of long term courses of 2 grams per day in patients with renal failure, a serum trough level may be warranted to avoid nephro-, neuro-, or ototoxicity. It is important to note that for the treatment of CDI, intravenous vancomycin is not appropriate because effective colonic concentrations are not obtained.

Common side effects associated with oral administration include bitter taste, nausea, vomiting, and stomatitis. Vancomycin can be with severe liver impairment, history of seizures, CHF, or other sodium-retaining states. Dose reductions should be considered in patients with severe liver impairment, CNS disease, or long term therapy in patients with severe renal impairment (CrCl <10mL/min). Disulfiram-like reactions to ethanol (flushing, headache, nausea, vomiting, sweating, or tachycardia) have been reported with oral metronidazole; therefore, alcoholic beverages should be avoided during therapy and for three days following regimen completion. Metronidazole should be taken on an empty stomach. If gastrointestinal upset occurs, it may be taken with food.

**Vancomycin (Vancocin®).** Vancomycin is the second-line agent for mild to moderate CDI, but preferred for severe and/or complicated CDI based on clinical study response rates. It was the first antibiotic with FDA approval for CDI. Vancomycin is more expensive than metronidazole ($600 to $1300, versus $15, for a 10-day course), and concerns of spreading VRE exist. It is also preferred for long term therapy and during pregnancy. When given orally, it is a pregnancy risk factor B (injection is category C). It does enter breast milk and is not recommended for nursing mothers. It may be administered through a nasogastric tube if oral administration is not possible. In addition, oral, nasogastric, and rectally administered vancomycin are not systemically absorbed from the gut; therefore, systemic laboratory monitoring does not generally apply. However, in some cases of long term courses of 2 grams per day in patients with renal failure, a serum trough level may be warranted to avoid nephro-, neuro-, or ototoxicity. It is important to note that for the treatment of CDI, intravenous vancomycin is not appropriate because effective colonic concentrations are not obtained.

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Common side effects associated with oral administration include bitter taste, nausea, vomiting, and stomatitis. Vancomycin can be
taken with food. Oral administra-
tion includes use of commercially
available oral capsules or an oral
solution that is compounded using
reconstituted powder for injection.
The latter is commonly used in
healthcare facilities as it is more
cost effective and appropriate for
nasogastric use.

Cholestyramine, colestipol, and
other anion-exchange resins bind
to vancomycin; concomitant use for
other anion-exchange resins bind
in patients with renal or hepatic
impairment and should, therefore,
be used with caution in these popu-
lations. The most common adverse
events reported with therapy
include headache, abdominal pain,
diarrhea, nausea, and vomiting.

Rifaximin (Xifaxin®). Rifaximin
is an antibiotic that is
currently indicated for the treat-
ment of traveler’s diarrhea caused
by noninvasive strains of E. coli
and reduction in the risk of overt
hepatic encephalopathy recur-
rence. It has been studied off-label
and prescribed as an alternative
for Clostridium difficile-associated
diarrhea. Rifaximin inhibits bacte-
rial RNA synthesis by binding to
bacterial DNA-dependent RNA
polymerase.

Rifaximin has been shown to be
effective against C. difficile in some
small case studies, but has also
revealed the development of resis-
tance. For example, eight patients
in one report who had four to eight
previous episodes of CDI and failed
combinations of standard therapy
(vancomycin, metronidazole) were
treated with an unconventional
regimen of vancomycin and ri-
famixin. The patients were treated
with vancomycin until symptoms
resolved followed by rifaximin for
14 days. The results were promis-
ing; however, large-scale trials are
needed.

Xifaxin is a poorly-absorbed
rifampin derivative. When used
off-label for CDI, the dose ranges
from 200 to 400mg two or three
times a day for 14 days. The cost
of therapy, dosed at 400mg three
times a day, is approximately $700.
It may be taken with or without
food. It is a pregnancy category risk
C; since excretion in breast milk is
unknown, it is not recommended
for nursing mothers. Rifaximin is
contraindicated in patients with
previous hypersensitivity to the
entity, a component of the formula-
ton, or other rifamycin antibiotics.
It should not be given with BCG,
the vaccine against tuberculosis.
Xifaxin has not been studied in
patients with renal impairment,
and should be used with caution
in patients with severe hepatic
impairment. The most common
adverse events experienced in-
clude peripheral edema, dizziness,
fatigue, ascites, nausea, headache,
pruritis, and abdominal pain.

New Drug: Fidaxomicin
(Dificid®)
Fidaxomicin is an oral macrolide
antibacterial agent that was FDA-
approved in 2011 for the treatment
of Clostridium difficile-associated
diarrhea in adults, making it the
second antibiotic with FDA approv-
al for this diagnosis. Dificid should
only be prescribed when there is
either strong suspicion or a con-
firmed diagnosis of CDI. Fidaxomi-
cin exerts its bactericidal activity
by inhibiting RNA synthesis by
RNA polymerases in susceptible
organisms (C. difficile).

Dificid was granted FDA ap-
proval based on the results of the
fidaxomicin versus vancomycin
for Clostridium difficile infection
clinical trial which was designed
to look for non-inferiority. Adults
with acute symptoms of C. difficile
infection and a positive result on
a stool toxin test were eligible for
the study. Patients were randomly
assigned to receive fidaxomicin
200mg twice daily or vancomycin
125mg four times a day orally for
10 days. The primary end point
was defined as clinical cure (res-
olution of symptoms and no need
for further therapy for CDI on the
second day after the end of ther-
apy). The secondary end points
were defined as recurrence of CDI (diar-
rhea and a positive result on a stool
infection) and global cure (cure
with no recurrence).

In the analysis of those pa-
Crohn’s disease were excluded from the study.

The recommended dosage for fidaxomicin is 200mg twice daily with or without food for 10 days. It is not systemically absorbed, and, currently, there are no contraindications for its use. Fidaxomicin is not appropriate for systemic infections. It is listed as pregnancy risk category B. Reproductive studies in rats and animals did not reveal evidence of harm to the fetus. However, there are no adequate, well controlled studies in pregnant women; therefore, fidaxomicin should only be used during pregnancy when clearly needed. It is presently unknown whether Dificid is excreted in breast milk; therefore, its use in nursing mothers warrants caution. There are currently no significant drug-drug interactions to report. It is metabolized by intestinal hydrolysis to a less active metabolite and largely excreted in the feces. No dosage adjustments are required for either renal or hepatic impairment.

The most common adverse reactions are nausea, vomiting, abdominal pain, gastrointestinal hemorrhage, anemia, and neutropenia.

Role of Probiotics
Probiotics are live, nonpathogenic bacteria that can colonize in the colonic mucosa. They are available over-the-counter, in health food stores or, more often, in fermented foods and dairy products such as yogurt. Various mechanisms have been proposed by which probiotics may be effective in the treatment and prevention of CDI. These include altering the intestinal flora, exerting antimicrobial activity, interfering with the binding of C. difficile toxins to the intestinal wall, and stimulating the immune system.

Probiotics are currently not recommended for primary treatment of CDI in most patients. They may be considered in patients with recurrent disease that is not severe, as long as there are no significant comorbidities. Probiotics may be used in combination with vancomycin. They are also not suggested for prevention in most patients, except for the elderly without significant comorbidities and who are also receiving antibiotic therapy. The two most commonly studied probiotics are the Lactobacillus species and Saccharomyces boulardii. Published clinical studies should be reviewed prior to recommending a probiotic product.

Cases of probiotic-associated bacteremia or fungemia have been reported. In most incidents, the susceptible patients had severe comorbidities, were on immunosuppressive therapy, had a recent surgical procedure, or had a recent...
prolonged hospitalization. The probiotics linked to these negative outcomes were most often *Saccharomyces boulardii* and *Lactobacillus rhamnosus GG*.

**Summary**

*Clostridium difficile* infection is a significant public health concern and the cause of increasing antibiotic-related diarrhea and mortality. Proper hand hygiene is the primary method for decreasing transmission among healthcare workers. Vancomycin and metronidazole are the two agents primarily outlined in SHEA/IDSA guidelines for treatment of CDI. They are the most widely studied agents, and those most commonly used for CDI. However, several newer agents have recently been investigated, including fidaxomixin (*Dificid®*) which was approved in 2011.

The author, the Ohio Pharmacists Foundation and the Ohio Pharmacists Association disclaim any liability to you or your patients resulting from reliance solely upon the information contained herein. Bibliography for additional reading and inquiry is available upon request.

This lesson is a knowledge-based CE activity and is targeted to pharmacists in all practice settings.
continuing education quiz

Clostridium difficile Infection Overview and Treatment with New Drug Fidaxomicin

1. Clostridium difficile infection was traditionally considered an infection acquired:
   a. in the community. b. in the hospital.

2. All of the following are characteristics associated with the newly recognized virulent C. difficile strain NAP1/BI/027 EXCEPT:
   a. produces up to 23 times more toxin A.
   b. produces binary toxin.
   c. is resistant to fluoroquinolones.

3. In addition to antimicrobial therapy, all of the following are potential risk factors for development of CDI EXCEPT:
   a. use of proton pump inhibitors.
   b. gastrointestinal procedures.
   c. ventilator use.
   d. length of hospital stay.

4. C. difficile transmission primarily occurs through which of the following routes?
   a. Oral-oral c. Vertical transmission
   b. Droplet d. Fecal-oral

5. Alcohol-based hand sanitizers are effective in killing C. difficile in its spore form.
   a. True b. False

6. The first step in treating CDI is to:
   a. conduct a stool culture on formed stool.
   b. conduct a stool culture on unformed stool.
   c. initiate treatment with metronidazole.
   d. discontinue therapy with the causative antimicrobial as soon as possible.

7. What is the drug of choice for an initial episode of mild to moderate CDI?
   a. Metronidazole c. Rifaximin
   b. Nitozoxanide d. Vancomycin

8. Which of following agents for CDI is preferred for long term therapy and during pregnancy?
   a. Metronidazole c. Rifaximin
   b. Nitozoxanide d. Vancomycin

9. For treatment of CDI, vancomycin can be administered by all of the following routes EXCEPT:
   a. intravenously. c. rectally.
   b. orally. d. via nasogastric tube.

10. Which of the following antibiotics is a synthetic antiprotzoal agent that has been shown to kill C. difficile in vitro testing?
    a. Metronidazole c. Rifaximin
    b. Nitozoxanide d. Vancomycin

11. Which of the following agents is a rifampin derivative and should not be given with BCG vaccine?
    a. Metronidazole c. Rifaximin
    b. Nitozoxanide d. Vancomycin

12. Patient counseling for fidaxomicin includes:
    a. it is pregnancy risk category D.
    b. it is indicated for individuals age 12 years and older.
    c. therapy should be discontinued as soon as diarrhea is resolved.
    d. it should not be used to treat systemic infections.

13. The recommended dosage for fidaxomicin is:
    a. 400mg three times a day for 10 days.
    b. 400mg three times a day for 14 days.
    c. 200mg twice daily for 10 days.
    d. 200mg twice daily for 14 days.

14. The most common reason for discontinuing fidaxomicin during clinical trials was:
    a. vomiting. c. abdominal pain.
    b. nausea. d. gastrointestinal hemorrhage.

15. The proposed mechanism of action for probiotics in treating and preventing CDI includes all of the following EXCEPT:
    a. altering intestinal flora.
    b. interfering with anaerobic metabolism of bacteria.
    c. stimulating the immune system.
    d. interfering with the binding of C. difficile toxins to the intestinal wall.

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