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
in sufficient disturbance of the intestinal microflora.

The second step is the acquisition of a toxigenic strain of *Clostridium difficile*. *C. difficile* spores are generally found in the hospital environment, with the risk of contamination being greatest in areas close to symptomatic patients. Most disease transmission is caused by the transient carriage on healthcare workers’ hands. The impaired protective barrier of the intestines then becomes colonized with *C. difficile*.

The third step is the development of clinical disease, though some patients may remain asymptomatic after colonization. The exact incubation time is not known, but is thought to be no longer than seven days. Development of symptomatic disease is determined by the patient’s ability to develop an immune response to the toxin.

**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 *Clostridium 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 *Clostridium 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
similar response rates, leading to mild disease, both treatments yield those treated with vancomycin. In a retrospective study, the time to resolution of diarrhea was significantly longer than in metronidazole-treated patients (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

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<tr>
<th>Clinical definition</th>
<th>Supportive clinical data</th>
<th>Recommended treatment</th>
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<td>Metronidazole: 500mg three times a day by mouth for 10 to 14 days</td>
</tr>
<tr>
<td>Initial episode, severe</td>
<td>Leukocytosis with WBC &gt;15 or SCr ≥1.5 times premorbid level</td>
<td>Vancomycin: 125mg four times a day by mouth for 10 to 14 days</td>
</tr>
<tr>
<td>Initial episode, severe, complicated</td>
<td>Hypotension or shock, ileus, megacolon</td>
<td>Vancomycin: 500mg four times a day by mouth or nasogastric tube, plus metronidazole 500mg every 8 hours intravenously. If complete ileus, consider adding rectal vancomycin</td>
</tr>
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</table>

| First recurrence | Same as initial episode |
| Second recurrence | Vancomycin in a tapered and/or pulsed regimen |

Adapted from 2010 practice guidelines for C. difficile infections in adults published by SHEA/IDSA.

**Table 2**

**Recommendations for the treatment of Clostridium difficile infection (CDI)**

- **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.

- **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. Common side effects associated with oral administration include bitter taste, nausea, vomiting, and stomatitis. Vancomycin can be
taken with food. Oral administration 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

Nittozanide (Alinia®). Nittozanide is a synthetic antiprotozoal agent that has been proposed as a treatment alternative for CDI. It is currently indicated for the treatment of diarrhea caused by *Giardia lamblia* or *Cryptosporidium parvum*. It exerts its activity by interfering with anaerobic metabolism of protozoa and bacteria. *In vitro* testing indicated that it was effective in killing *C. difficile*. In addition, favorable kinetics for CDI include that nittozanide is largely nonabsorbed by the gastrointestinal tract and two-thirds is excreted in feces. Clinical data has reported that when used to treat CDI, it is at least as effective as metronidazole and is effective for patients who experience treatment failure with metronidazole.

Musher et al. conducted the first prospective, double-blind, randomized controlled trial comparing nittozanide to vancomycin. Fifty patients were included in the trial and received either Alinia 500mg by mouth twice daily or vancomycin 125mg by mouth four times a day. In those who completed the therapy, response rates were 87 percent (20 of 23 patients) in the vancomycin group and 94 percent (17 of 18 patients) in the nittozanide group. The authors state that this small sample does not confirm noninferiority of Alinia to vancomycin.

The cost of Alinia for 10 days of therapy is approximately $400 to $500. Based on cost, the authors suggest that nittozanide should not replace metronidazole for treatment of outpatients with mild to moderate disease. A much larger study is required before it may be considered as a substitute for vancomycin for severe CDI.

Nittozanide is categorized as pregnancy risk factor B, and its excretion in breast milk has not been studied and is unknown. It is contraindicated in patients with a history of hypersensitivity to the agent or any component of the formulation. It has not been studied in patients with renal or hepatic impairment and should, therefore, be used with caution in these populations. 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 treatment of traveler’s diarrhea caused by noninvasive strains of *E. coli* and reduction in the risk of overt hepatic encephalopathy recurrence. It has been studied off-label and prescribed as an alternative for *Clostridium difficile*-associated diarrhea. Rifaximin inhibits bacterial 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 resistance. 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 rifaximin. The patients were treated with vancomycin until symptoms resolved followed by rifaximin for 14 days. The results were promising; 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 formulation, 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 include 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 approval for this diagnosis. Dificid should only be prescribed when there is either strong suspicion or a confirmed diagnosis of CDI. Fidaxomicin exerts its bactericidal activity by inhibiting RNA synthesis by RNA polymerases in susceptible organisms (*C. difficile*).

Dificid was granted FDA approval 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 (resolution of symptoms and no need for further therapy for CDI on the second day after the end of therapy). The secondary end points were defined as recurrence of CDI (diarrhea and a positive result on a stool toxin test within four weeks after treatment) 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 Difid 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 reason for discontinuation of fidaxomicin during clinical trials was vomiting. Other gastrointestinal adverse events include nausea, gastrointestinal hemorrhage, and abdominal pain. Difid is also associated with hematologic events such as anemia and neutropenia.

Fidaxomicin costs approximately $2700 for a 10-day course of therapy. Its benign safety profile and initial clinical studies indicate that it has a promising future in treating CDI; however, its current place in therapy has not been established at the time of writing this lesson. Counseling points are included in Table 3.

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. When probiotics are ingested, it is thought that they temporarily colonize the gut creating competition for nutrients and epithelial adhesion leading to an unfavorable environment for C. difficile to flourish. Despite the number of clinical trials that have been conducted, the role of probiotics remains uncertain. Not only have results been conflicting, but it is difficult to extrapolate the results from one probiotic formulation to another. The trials have been conducted with products containing distinctive probiotic species with various characteristics (i.e., acid resistance, colonization of lower intestinal tract, and cytokine secretion) and quantities. In addition, since probiotics are categorized as dietary supplements, the manufacturers are not required to prove safety or evidence of good manufacturing practices. Hence, probiotics’ product labeling may not accurately reflect the number of live cultures listed.

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.

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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  
   b. Vertical transmission  
   c. 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  
   b. Nitozoxanide  
   c. Rifaximin  
   d. Vancomycin

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

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

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

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