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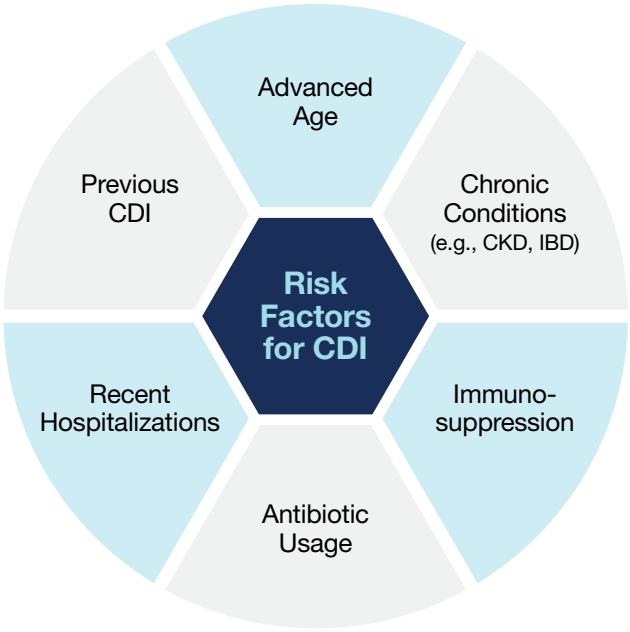
Focus on *Clostridium difficile* Infection – Part 2: Risk and Risk Reduction

- by Mary Mehrabian and Allen Lefkovitz

Following last month's article addressing diagnosis and treatment of *Clostridium difficile* infection (CDI), this month's focus article will address risk and risk reduction of CDI while concentrating on antibiotic stewardship and infection control as well as the use of probiotics. Understanding the risk factors which contribute to CDI, the principals of antibiotic stewardship, and what prevention measures can be taken are important steps to preventing and decreasing the incidence of new infections.

Figure 1



Risk and Risk Reduction

Clostridium difficile is a widely recognized health care associated pathogen which may cause significant morbidity, mortality and health care costs. Common risk factors for CDI are depicted in Figure 1. Within the updated Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA) CDI guidelines published in February 2018, three recommendations surrounding antibiotic stewardship are made.

1 Implement an antibiotic stewardship program

As stated in "The Core Elements of Antibiotic Stewardship for Nursing Homes" from the Centers for Disease Control and Prevention (CDC), 70% of residents in nursing homes receive one or more courses of systemic antibiotics per year and 40-75% of these agents may be unnecessary or inappropriate. Antibiotic stewardship is defined by the CDC as "optimiz[ing] the treatment of infections while reducing adverse drug reactions associated with antibiotic use." Long-term care (LTC) facilities should have policies in place to ensure that residents are started on antibiotic therapy only if needed (e.g., meeting a minimum prescribing criteria) and should review antibiotic appropriateness and resistance patterns on a regular basis.

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2 Minimize the frequency and duration of high-risk antibiotic therapy and the number of antibiotic agents prescribed, to reduce CDI risk.

The single most modifiable risk factor for the CDI is the use of antibiotics

Nearly all antibiotics increase the risk of developing CDI. However, certain classes of antibiotics have an increased risk for CDI as outlined in Figure 2.

Figure 2. Commonly used antibiotic therapies frequently associated with *Clostridium difficile* infection

Fluoroquinonlones (e.g., levofloxacin)	**Penicillins** (e.g., amoxicillin)
Cephalosporins (especially 3rd and 4th generation; e.g., cefepime)	**Clindamycin**

In addition to antibiotics, other classes of drugs, such as proton pump inhibitors (PPI), have been associated with developing CDI, but have not been definitively proven as a cause. Guidelines do not advocate discontinuation of PPI for prevention but, do recommend that unnecessary PPI use should be discontinued.

3 Antibiotics to be targeted should be based on the local resistance patterns and the *C. difficile* strains present. A program that responsibly restricts empiric use of some antibiotics [e.g., fluoroquinolones, clindamycin, cephalosporins (except for surgical antibiotic prophylaxis)] should be considered. Every LTC facility, at a minimum, should have proper surveillance in place to detect elevated rates of CDI. In order to track CDI rates and antibiotic resistance, LTC facilities should consider reporting to the National Healthcare Safety Network (https:www.cdc.gov/nhsn/ltc/cdiff-mrsa/index.html).

Infection Control

Early detection, contact precautions and isolation are key for infection control and numerous strategies should be considered, such as the following:

Residents with CDI should be placed in a private room with a dedicated toilet, whenever possible
- If private rooms are limited, residents with stool incontinence should be prioritized
- Isolation should continue until at least 48 hours after the diarrhea has resolved; in facilities with higher infection rates, contact precautions may be in place until discharge

Initiate contact precautions for those presenting with suspected CDI pending diagnostic test results

All healthcare workers should wear gloves and gowns on entry to a room and while taking care of residents with CDI

Limit the use of non-disposable medical equipment (e.g., electronic rectal thermometers, stethoscopes)

Hand hygiene should be performed before and after any contact with an infected person
- in the absence of an outbreak, wash hands with soap and water or use alcohol based products
- in outbreaks or in facilities with higher infection rates, wash hands with soap and water over alcohol based products, especially if there is direct contact with feces or fecal contaminants

Daily room cleaning and thorough cleaning following discharge should be performed with sporicidal agents as *Clostridium difficile* spores can live on surfaces for several months

Use of Probiotics

Probiotics are live microorganisms (e.g., *Lactobacillus GG*), which when administered in adequate amounts, may confer a health benefit on the host. It is proposed that probiotics work by altering or helping to correct the intestinal flora. Although probiotics are supplements that are unregulated by the FDA, there is likely little harm of probiotic use by normal healthy adults. However, some studies report the possibility of bacteremia or fungemia with those that are immunosuppressed, elderly with severe comorbidities, or those with frequent hospitalizations.

The IDSA/SHEA CDI guidelines state "There are insufficient data at this time to recommend administration of probiotics for primary prevention of CDI." More recently, SHEA reported on two studies that demonstrated that multi-strain probiotics might be a cost effective treatment in the prevention of CDI (see https://www.shea-online.org/index.php/journal-news/press-room/press-release-archives/588-probiotics-useful-in-the-fight-against-c-difficile). There are a few studies which demonstrate a potential benefit of probiotics in the secondary prevention of CDI with the use of strains such as *Saccharomyces boulardii* in nonsevere CDI without significant co-morbid conditions. However, there is a lack of consistency in the studies in terms of probiotic strains, dose and duration.

The best way to prevent new cases and decrease the spread of CDI, is through:

1. Recognition of risk factors
2. Implementation of facility antibiotic stewardship and surveillance programs
3. Instituting infection control procedures.

Medication Safety

New Warning for Lamictal (lamotrigine)

- by Richard Kilmartin

In April 2018, the U.S. Food and Drug Administration warned that lamotrigine can cause hemophagocytic lymphohistiocytosis (HLH), a rare but potentially fatal complication. Lamotrigine is commonly used for the management of seizures and bipolar disorder. Lamotrigine already carries a Boxed Warning about serious complications, including life-threatening rashes.

HLH is an abnormal immune response where healthy tissues and cells are attacked by a person's immune system, resulting in inflammation and organ damage. Symptoms may occur within days to weeks following initiation of lamotrigine (see Table 1). Treatment is aimed at suppressing the immune response, addressing underlying triggers, and decreasing systemic inflammation.

Health care professionals should be aware that HLH can occur at any age and constitutes a medical emergency. Prompt recognition and early treatment are important for improving HLH outcomes and decreasing mortality. Diagnosis can be complicated as early signs and symptoms are often nonspecific (e.g., fever, rash).

Severely ill patients with multiorgan involvement or unexplained clinical decline who are receiving lamotrigine should be evaluated for the possibility of HLH. Lamotrigine should be stopped if HLH is suspected, or at the first signs of rash; however, clinicians should be aware that stopping lamotrigine may result in seizures and/or mood lability. When possible, an alternative treatment for the underlying condition should be considered.

Table 1. Signs and Symptoms Associated with HLH

Fever greater than 101˚ F (38.3˚ C)	Swollen lymph nodes
Pain, tenderness or swelling in the upper right abdomen	Skin rash
Blood dyscrasias (e.g., hemoglobin < 9 g/dL, platelets < 100,000/µL, ANC < 1000/µL)	Yellowing of the skin or eyes
Elevated triglycerides or low fibrinogen levels	Unusual bleeding
Nervous system symptoms (e.g., difficulty walking, visual changes, seizures)	Elevated serum ferritin

Additional information about this new warning is available at https://www.fda.gov/Drugs/DrugSafety/ucm605470.htm

NEW Generic Medications

- by Allen Lefkovitz

Generic Name	Brand Name	Date Generic Available
Miglustat 100 mg Capsule	Zavesca® Capsule	4/25/18
Praziquantel 600 mg Tablet	Biltricide® Tablet	4/20/18

NEW Drug

Andexxa™ (coagulation factor Xa [recombinant]) Injection

- by Dave Pregizer

Brand Name (Generic Name)	**Andexxa [an DEX a] (coagulation factor Xa [recombinant])**
How Supplied	Lyophilized powder in single-use vials of 100 mg
Therapeutic Class	Recombinant modified human Factor Xa (FXa) protein
Approved Indication	For patients treated with rivaroxaban and apixaban, when reversal of anticoagulation is needed due to life-threatening or uncontrolled bleeding.
Usual Dosing	Dosage is based on the specific FXa inhibitor, dose, and timing of last dose. There are two dosing regimens. Low dose: initial bolus of 400 mg at a target rate of 30 mg/min followed by a continuous IV infusion of 4 mg/min for up to 2 hours. High dose: initial bolus of 800 mg at a target rate of 30 mg/min followed by a continuous IV infusion of 8 mg/min for up to 2 hours.
Select Drug Interactions	None reported
Most Common Side Effects	Urinary tract infections, pneumonia, and infusion-related reactions.
Miscellaneous	Boxed Warning: Thromboembolic risk, ischemic risk, cardiac arrest, and sudden death. Andexxa is not indicated for the treatment of life-threatening or uncontrolled bleeding related to edoxaban, enoxaparin or other FXa inhibitors. To reduce the risk of thrombosis, resume anticoagulant therapy as soon as medically appropriate following treatment with Andexxa.
Website	andexxa.com

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