Section 10: Antimicrobial Stewardship and *Clostridium difficile* Infection: A Primer for the Infection Preventionist

Antimicrobial stewardship may be a relatively new addition to the job responsibilities of the IP. The discussion of antimicrobial use and its impact on patients in all healthcare settings in this section is focused solely within the context of *C. difficile*. The broad term "antimicrobial stewardship" is used in place of "antibiotic stewardship," as development of a stewardship program ideally includes all antiviral and antifungal agents as well as antibiotics. As antibiotics are the antimicrobial agents effective against bacteria, the term antibiotic is used most often in the discussion of *C. difficile* infection.

Role of antibiotic use in the occurrence of CDI

Because CDI is nearly always a complication of antibiotic use, the development of a healthcare facility program to ensure appropriate antibiotic use is considered an important prevention intervention.[1-4] Figure 10.1 represents the different phases of *C. difficile* infection of the colon, starting with a normal colonic environment (phase A) through the development of pseudomembranous colitis (phase D).

The most important protection mechanism against CDI in humans is the normal gut flora. These bacteria reside in the gastrointestinal tract and prevent pathogens from attaching, multiplying, and producing disease.[5,6]
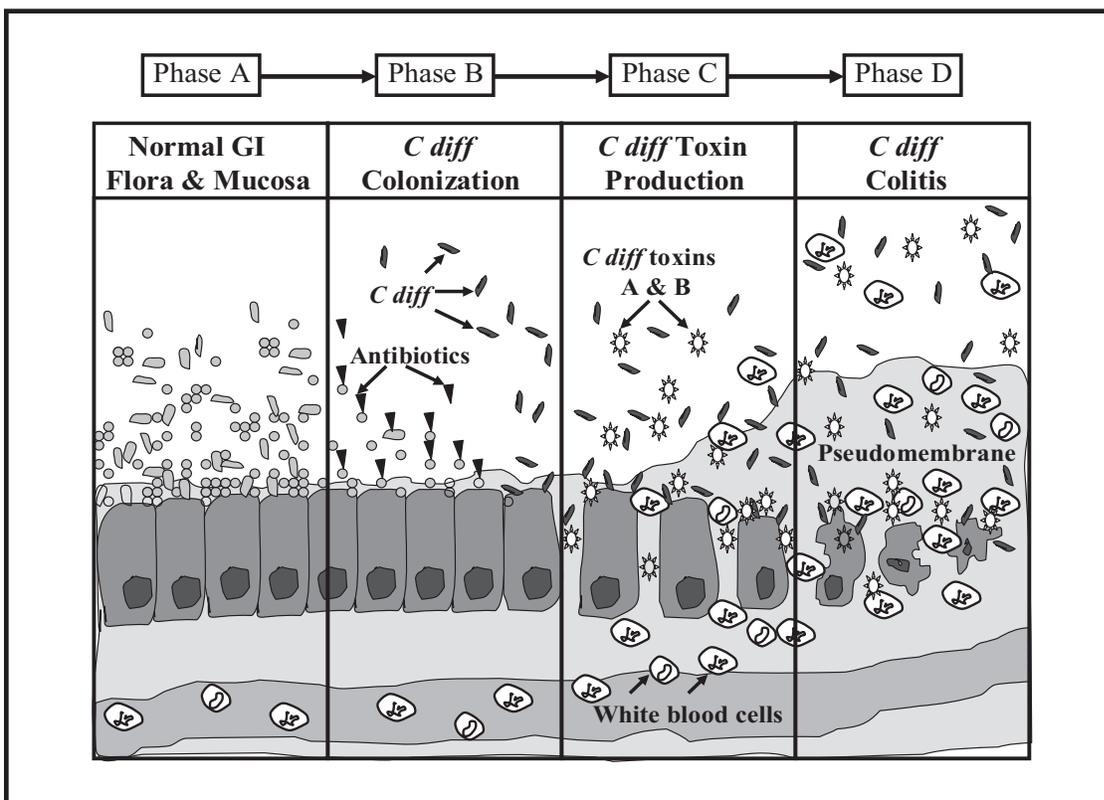
Normal colonic flora

The hundreds of trillions of bacteria that make up our normal gastrointestinal flora are an important defense mechanism against intestinal pathogens.[5,6] This ecosystem of bacteria is called the human gastrointestinal microbiome. Some of the normal bacterial flora is attached to receptors on the epithelial cells in the colon, whereas other bacteria are present in the lumen of the gastrointestinal tract (Figure 10.1, phase A). In order for *C. difficile* to maintain a presence, the normal flora must be depleted. Due to the diverse bacterial species in the human colon, it has been difficult to identify which particular organisms are responsible for the protective effect against *C. difficile*. The exact mechanism by which an intact gastrointestinal flora protects against *C. difficile* colonization is not completely understood, but several mechanisms have been proposed. To cause colonization or an infection, *C. difficile* needs to attach to receptors in the human gastrointestinal cells. If these receptors are occupied by organisms of the normal gastrointestinal flora, *C. difficile* strains reaching the gut mucosa will have no place for attachment and will not be able to survive.

In addition to preventing colonization by competing for attachment sites, the normal flora may prevent colonization by depriving *C. difficile* of essential nutrients. The normal flora may also antagonize *C. difficile* through the production of substances that inhibit or kill *C. difficile*. Antibiotics may also alter the colonic microenvironment by changing the local protein composition or amount of local mucus production, which may aid the survival of *C. difficile*.

Figure 10.1. Phases of pathogenesis of *C. difficile* colitis.

Antibiotic collateral damage

As mentioned previously, the normal gastrointestinal flora are the main protection mechanism of the host to prevent colonization and infection with pathogens such as *C. difficile*. If this microbiome is disrupted (Figure 10.1, phase B), *C. difficile* can attach to the gastrointestinal epithelial cells, produce toxin (Figure 10.1, phase C), and cause disease (Figure 10.1, phase D). Because antibiotics kill bacteria and are not specific to one particular bacterium, they all have the ability to disrupt the balance of bacteria in the microbiome. The propensity of a particular antibiotic to alter the gastrointestinal flora can be defined as antibiotic "collateral damage."[7]

The extent of damage depends upon a number of antibiotic-specific factors such as: 1) the spectrum of activity, 2) duration of therapy, 3) the amount of the antibiotic that reaches the colonic environment, 4) the activity of the antibiotic under the anaerobic conditions of the colon, 5) antibiotic dose, 6) the route of administration, and 7) antibiotic excretion in the bile. Antibiotic collateral damage is largely due to the killing of normal colonic flora, but antibiotics may cause collateral damage by altering other colonic factors beyond bacteria that may play an important role in local defense mechanisms against *C. difficile*. In the next sections, we review the major factors of antibiotics that play a role in the disruption of the normal colonic flora, leading to colonization and/or infection with this pathogen.

Antibiotic spectrum of activity and duration of therapy

All antibiotics produce disruption of the colonic flora, but they are not equal in their capability to cause collateral damage. The first two elements that need to be considered when evaluating the risk for CDI produced by a particular antibiotic

include antibiotic spectrum and duration.[8] The first is the level of risk produced by a particular antibiotic, defined by the antibiotic spectrum of activity. As the titles suggest, broad-spectrum antibiotics kill a variety of different bacteria, whereas narrow-spectrum antibiotics kill a much smaller variety. In this regard some antibiotics will place the patient at low, intermediate, or high risk for development of CDI.

The second factor to be considered is the number of days that the patient will be at risk for development of CDI. Greatest days at risk for colonization occur during the time that the patient is receiving antibiotic therapy and up to 5 to 10 days after discontinuation of antibiotics, although the risk may extend for 3 months or more. The longer a patient is treated with an antibiotic, the more normal flora will be killed.[8]

These two factors combined are critical in the pathogenesis of *C. difficile*. For example, a patient who receives a narrow-spectrum antibiotic for less than 1 day, such as one dose of a first-generation cephalosporin for surgical prophylaxis, will be considered to have a low level of risk and a short duration of risk. If the same patient is given surgical prophylaxis with an unnecessarily broad-spectrum antibiotic (e.g., a carbapenem), the level of risk can move from low to high without any additional clinical benefit from that broad-spectrum antibiotic. Extension of surgical prophylaxis with a first-generation cephalosporin for multiple doses that continue beyond the day of surgery will also increase the risk of CDI by increasing the number of days that the patient will be at risk. Even though all antibiotic therapy, appropriate or inappropriate, will place the patient at risk for CDI, the prolonged use of broad-spectrum antibiotics is an unnecessary additional risk factor that may be prevented.

The most common inappropriate antibiotic use that places a patient at increased risk is the continuation of broad-spectrum antibiotics after the etiology of infection has been identified,

and the pathogen is found to be susceptible to a narrower-spectrum antibiotic. For example, in a patient with a prolonged ICU stay that developed a ventilator-associated pneumonia (VAP), it would be appropriate to start empiric therapy with a broad-spectrum regimen to cover the possibility of resistant Gram-positive as well as Gram-negative bacteria (e.g., vancomycin plus piperacillin/tazobactam). If respiratory or blood cultures identify an MSSA as the etiology of VAP, the continuation of the initial broad-spectrum coverage should be considered inappropriate. In this clinical scenario, antibiotic therapy should be "de-escalated" to a regimen that targets MSSA such as nafcillin or cefazolin. Initial empiric broad-spectrum therapy in hospitalized patients at risk of infections due to resistant organisms should always be followed by de-escalation of therapy if resistant organisms are not identified as the etiology of infection. Because lack of de-escalation is a common reason for inappropriate antibiotic use, the antibiotic stewardship program should develop strategies to prevent the collateral damage associated with lack of appropriate de-escalation of antibiotic therapy. The antibiotic program should intervene to correct other poor antibiotic practices that are associated with collateral damage, such as the use of antibiotics directed to treat bacterial colonization (versus infection) or contamination (e.g., blood cultures) as well as the use of antibiotics in patients without documented infections.

Antibiotic uptake in the colon

Different antibiotics have a varied uptake in different areas of the body. For example, oral vancomycin is not absorbed systemically and will therefore only kill bacteria in the gut. Intravenous vancomycin, on the other hand, by definition of the route of administration, is systemically available. However, IV vancomycin does not reach adequate concentrations in the gastrointestinal tract and consequently may not be able to kill a significant amount of the normal gastrointestinal flora. The availability of different antibiotics to

different body sites is an important consideration for antimicrobial stewardship activities, as availability in the colon provides more disruption of the normal flora.

Activity of antibiotics under anaerobic conditions

A very limited amount of oxygen is available to organisms living in the colon. Because of this, organisms living primarily in the colon, such as _C. difficile,_ are only capable of surviving in anaerobic conditions. This is a critical factor for the treatment of CDI, as only antibiotics with activity against anaerobic organisms are able to kill _C. difficile_. Additionally, this is an important factor for antimicrobial stewardship programs. Antibiotics that have anaerobic activity will kill more of the normal colonic flora (as most are anaerobic), leaving room for attachment and growth of _C. difficile_. As before, it is important to consider the spectrum of activity and duration of treatment in conjunction with this factor. A narrow-spectrum antibiotic with good anaerobic coverage will be less of an issue than a broad-spectrum antibiotic with limited anaerobic coverage. Although the narrow-spectrum antibiotic will kill anaerobes, it will only kill a limited variety. The broad-spectrum antibiotic will kill the anaerobes as well, but it will kill a wide variety, leaving the colonic environment more hospitable for _C. difficile._

Antibiotic dose

The dose of antibiotic administered is another important consideration for antimicrobial stewardship programs. Over- or underdosing may be considered inappropriate in many situations. A dose greater than necessary may kill a greater number of normal flora, whereas a lower dose may not appropriately kill the bacteria causing the infection. This cycle may lead to the switching to or addition of a new antibiotic, or the need for a longer duration of therapy. Each of these factors may contribute to CDI.

Antibiotic routes of administration

As mentioned previously, the route (typically intravenous versus oral) of administration of antibiotics may confer a different risk to the normal flora. Oral antibiotics may pose a greater risk to the normal gastrointestinal flora, as incompletely absorbed oral antibiotics may have direct access to these bacteria.[9] Members of antimicrobial stewardship programs should be aware of these risks to ensure the most effective and least detrimental route of antibiotic administration is utilized.

Antibiotic excretion in the bile

Antibiotics excreted in the bile at a high concentration have been shown to deplete more of the normal flora than those that are not. This is due to high intraintestinal concentrations of these drugs. Antibiotic excretion in the bile may be considered a higher priority than oral versus intravenous administration as well. Intravenous antibiotics excreted in the bile at high concentrations may kill more of the normal flora than incompletely absorbed oral antibiotics.[10,11]

Role of antimicrobial stewardship in prevention of colonization and infection

Colonization with _C. difficile_ may occur when the normal flora is depleted and the organism is introduced into the gastrointestinal tract. Interventions to improve the practice with regard to the previously mentioned factors will help to reduce the excessive depletion of the normal flora. However, antimicrobial stewardship practices will not prevent introduction of the organism into the gastrointestinal tract. Basic infection prevention practices are necessary for this essential component of _C. difficile_ prevention.

Once a patient is colonized with _C. difficile_, the patient may progress to develop _C. difficile_ colitis

or may remain colonized without developing disease. Lack of disease may be due to colonization with a *C. difficile* strain that does not produce toxins.[12] Once the patient is colonized with a nontoxigenic strain, the patient may be less likely to be colonized with another strain—one that may be toxigenic. It is considered that the initial strain may occupy receptors than become unavailable to a new strain. The use of metronidazole in a patient colonized with a nontoxigenic *C. difficile* strain may favor development of *C. difficile* colitis by killing the nontoxigenic strain and allowing colonization and infection due to a toxigenic strain. This is the reason behind laboratory testing for *C. difficile* toxins as opposed to solely testing for *C. difficile* antigens (e.g., glutamate dehydrogenase). Antigen testing does not differentiate between toxigenic and nontoxigenic strains.[13] Identification of the organism through antigen testing alone will provide clinicians with unnecessary data and may result in unnecessary antimicrobial treatment. However, a positive test for *C. difficile* toxin in the stool is not by itself indication for an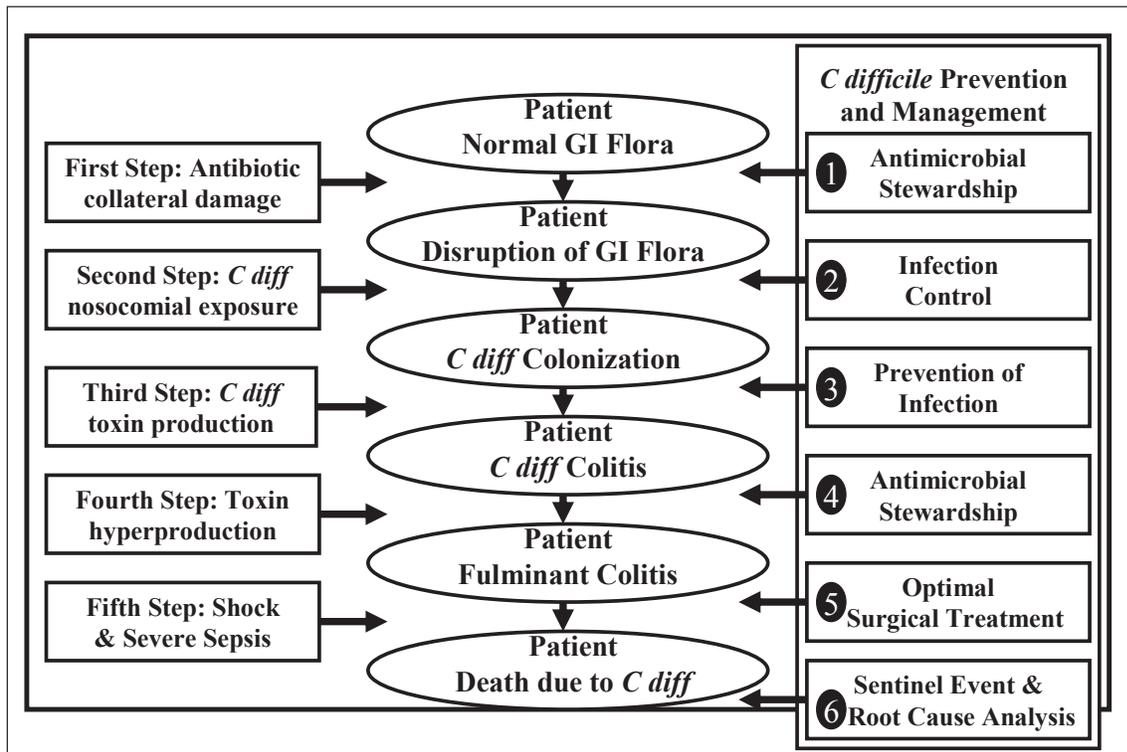tibiotic therapy. A patient who is asymptomatic but has a positive *C. difficile* test should be considered a carrier and antibiotic therapy is not indicated. The inappropriate use of metronidazole or vancomycin may favor development of disease or MDROs in a patient who is only a carrier.

Role of antimicrobial stewardship in treatment of infection

Once a patient is diagnosed as having CDI, antimicrobial stewardship is important to achieve optimal medical therapy. This is represented in the *C. difficile* prevention activities (Figure 10.1) as the fourth level of intervention. There are three strategies that can be considered for the management of a patient with *C. difficile* colitis: 1) killing of *C. difficile*, 2) blocking toxin, and 3) restoring normal flora.

Killing of *C. difficile* in the colon can be achieved with the use of a number of antibiotics, most

Figure 10.2. Activities to prevent and manage *C. difficile* infection in healthcare settings.

commonly oral metronidazole or oral vancomycin. In patients treated with oral metronidazole, the stool metronidazole levels decrease as colonic inflammation improves, when the patient moves from liquid stools to more formed stools. Oral vancomycin maintains similar concentrations throughout therapy. In patients with an ileus, a significant delay in the passage of antibiotics from the stomach to the colon may occur. When intravenous therapy is necessary, metronidazole can be used because it is excreted by the bile and by the inflamed colonic mucosa, achieving fecal levels sufficient to treat CDI. On the other hand, intravenous vancomycin is not excreted into the colon and cannot be used to treat CDI. If oral vancomycin cannot be used, vancomycin enemas are an alternative to kill *C. difficile* in the colon. Even when appropriate metronidazole or vancomycin therapy is used, relapse of CDI is expected to occur in 10 to 25 percent of the patients. A relatively new agent, fidaxomicin, is also available for the treatment of *C. difficile* infections. This agent has been shown to be as effective as the other available agents, but may improve patient outcomes through decreasing the likelihood of disease relapse.[14]

Blocking *C. difficile* toxin in the colon with the anion-binding resins colestipol and cholestyramine has been investigated but this strategy is not effective as primary therapy for CDI. The toxins may be blocked by administration of intravenous immunoglobulin because commercially available intravenous formulations contain antibodies to toxin A and B. This approach is sometimes considered for patients with severe disease.

Restoration of the normal colonic microenvironment is of paramount importance in the management of CDI. A critical step in the restoration of normal colonic flora is an evaluation of the patient to determine if current antibiotic therapy could be discontinued. In some patients continuation of antibiotic therapy will be necessary to complete treatment of an infection. In these cases the antimicrobial team, considering the type of infection, can suggest continuation of therapy with an antibiotic that produces minimal collateral damage of the gastrointestinal flora. In an attempt to restore the colonic microenvironment, the oral administration of microorganisms with beneficial properties, or probiotics, has been investigated in patients with CDI. The theoretical benefits of probiotics in patients with CDI may include the suppression of *C. difficile* growth, the binding of probiotics to epithelial cells to block receptors for *C. difficile* binding, improvement of intestinal barrier function, and favorable modulation of the local immune system. Because the data from clinical studies of probiotics in patients with CDI is inconclusive, probiotics are not considered current standard of care in the management of patients with CDI.[15] In an effort to restore normal colonic flora, the administration of the entire fecal flora from a healthy individual, an approach referred to as fecal transplant, has been investigated. Although the data are largely limited to case series, the fecal transplant has been shown to be more than 90 percent successful at treating relapsing CDI.[16]

Elements of an antimicrobial stewardship program

The goal of an antimicrobial stewardship program is to optimize the use of the right drug, for the right purpose, at the right dose, and for the right duration in an effort to promote judicious use of the antimicrobial agent. Discussion of what constitutes an effective stewardship program is beyond the scope of this document but the basics include elements such as 1) written guidelines for use of specific antimicrobials that have been developed using evidence as a basis and involve input from clinicians; 2) accurate microbiologic results and prompt reporting of those results; 3) antibiograms compiled and disseminated in a manner that enables clinicians to select the appropriate agent(s) for empiric therapy; 4) systems that minimize opportunities for inappropriate duration of therapy; 5) processes that actively support de-escalation of therapy to a more narrow-spectrum agent; 6) feedback on adherence to guidelines; and 7) monitoring of

systems that support the total program. Thorough discussions of the key elements of an antimicrobial stewardship program can be found in other sources.[17,18] These examples are but a few of the important elements for an effective antimicrobial stewardship program and serve to demonstrate the scope of activities and depth of administrative support necessary for success.

Infections due to *C. difficile* are increasing in incidence and severity in healthcare settings. These infections are associated with increased patient morbidity and mortality. It is concerning that patients admitted to a healthcare facility for noninfectious diseases can die during hospitalization due to an infection produced by *C. difficile*. Considering the critical role that antibiotic use plays in the pathogenesis of CDI, it is important for all healthcare facilities and practitioners to implement an antimicrobial stewardship program with a focus on CDI prevention, control, and treatment. A combination of optimal infection prevention activities and antibiotic control is necessary to prevent the transmission of *C. difficile* and development of CDI.

To maintain a comprehensive approach to optimizing use of antimicrobial agents, it is important that the IP understands the components of an antimicrobial stewardship program and the organizational support necessary for its success.

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