Review of *Clostridium difficile*

One of the most common adverse effects associated with antibiotic therapy is diarrhea. Antibiotics cause diarrhea by upsetting the balance of the normal colonic flora. Antibiotic-associated diarrhea is often self-limiting and moderate in severity; however, colitis and systemic symptoms may occur. *Clostridium difficile* (C. difficile), a gram-positive anaerobic pathogen, is responsible for about 25% of cases of antibiotic-associated diarrhea and 50% to 75% of cases of colitis due to antibiotic use. Presence of *C. difficile* is generally linked to more severe diarrhea/colitis, and the pathogen is the most common cause of nosocomial diarrhea. The incidence of *C. difficile* has risen in recent years due to increased use of antibiotics. Most currently available antibiotics have been linked to causing *C. difficile*, but the most common culprits are clindamycin, cephalosporins, and penicillins.

Carriage of *C. difficile* is common in infants and children and hospitalized patients. The pathogen is occasionally (3% to 5%) isolated in stool samples from otherwise healthy adults. Interestingly, infants and young children rarely suffer from colitis due to *C. difficile* possibly because they have increased antibodies to the pathogen or because the pathogen can not bind to the immature colonic mucosa in this population. On the other hand, diarrhea and colitis are prevalent in debilitated, elderly, cancer, surgical, burned, and hospitalized patients who are colonized with *C. difficile*. The etiology behind the development of diarrhea and colitis due to *C. difficile* mimics that of antibiotic-induced diarrhea; an abundance of *C. difficile* in the gastrointestinal tract occurs when antibiotics disrupt the equilibrium of the normal gut flora causing an overgrowth of the pathogen. *Clostridium difficile* has been shown to produce 2 toxins (A and B) that work synergistically to cause infection. Toxin A is an enterotoxin and is mostly responsible for the diarrhea associated with the disease. Toxin B is believed to be associated with damage to the cellular components. Generally both toxins are present in infected individuals; however, toxin A-negative/toxin B-positive disease also occurs.

**Clinical presentation**
Onset of symptoms may be abrupt, within days of the start of antibiotic therapy, or prolonged, presenting for up to 8 weeks after treatment is discontinued. Diarrhea associated with *C. difficile* is generally characterized as mucoid, foul-smelling, watery, and green in color; however, patients with severe disease in the cecum or right colon may not experience diarrhea. Symptoms vary based on severity of the disease and are summarized in table 1.

**Diagnostic Testing**
Diagnosis of *C. difficile*-associated diarrhea is primarily based on clinical symptoms and stool assays for presence of the pathogen or toxins. Endoscopy may also be performed; however, this option is expensive and generally reserved for specific clinical scenarios when rapid diagnosis is required. Features of select diagnostic tools used to detect *C. difficile* are summarized in table 2.

**Treatment**
Treatment of *C. difficile* diarrhea is well established and is based on guidelines from the Infectious Diseases Society of America,
Table 1. Select clinical manifestations of \textit{C. difficile}.*

<table>
<thead>
<tr>
<th>Mild Disease</th>
<th>Moderate Disease</th>
<th>Severe Colitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild lower abdominal cramping</td>
<td>Abdominal distension and cramps</td>
<td>Severe abdominal pain</td>
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<tr>
<td></td>
<td>Fever</td>
<td>High fever</td>
</tr>
<tr>
<td></td>
<td>Volume depletion</td>
<td>Volume depletion</td>
</tr>
<tr>
<td></td>
<td>Profuse diarrhea</td>
<td>Profuse diarrhea (+ or -)</td>
</tr>
<tr>
<td></td>
<td>Fecal leukocytes</td>
<td>Fecal leukocytes</td>
</tr>
<tr>
<td></td>
<td>Moderate leukocytosis</td>
<td>Severe leukocytosis</td>
</tr>
<tr>
<td></td>
<td>Nausea, anorexia</td>
<td>Nausea, anorexia</td>
</tr>
<tr>
<td></td>
<td>Malaise</td>
<td>Malaise</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Toxic megacolon</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mucosal edema</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Thickened colon</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Colonic bleeding</td>
</tr>
</tbody>
</table>

*Adapted from Arch Intern Med 2001;161:525-33.

guidelines supported by the American College of Gastroenterology, and other guidelines from various groups. First and foremost, consideration should be given to discontinuing precipitating antibiotics, and supportive care (fluid/electrolyte replacement) should be implemented. Antiperistaltic and opiate medications should be avoided as they may worsen the disease process. Metronidazole and vancomycin, both given orally are the agents of choice in treatment of \textit{C. difficile}; however, metronidazole is preferred in most cases because it is less expensive and avoids promoting vancomycin resistance. Furthermore, availability concerns exist for oral vancomycin. The oral solution has been discontinued, and oral capsules are currently on back order. It is anticipated that adequate supplies will be available in October 2003. If vancomycin capsules are not available, the injection form can be given orally. The injection should be diluted in accordance with the prescribing information to a concentration of 100 mg/mL; the solution is further diluted with 30 mL (1 ounce) of water prior to oral administration.

Intravenous metronidazole (500 mg given 3 times/day) should be reserved for patients who can not take oral medications. Of note, use of intravenous vancomycin is not appropriate for treatment of \textit{C. difficile} because adequate concentrations will not be achieved in the colon.

Table 2. Diagnostic testing of \textit{C. difficile}.

<table>
<thead>
<tr>
<th>Test</th>
<th>Detects</th>
<th>Comments</th>
</tr>
</thead>
</table>
| Cytotoxin assay | Toxin B | - Gold standard  
- High sensitivity/specificity  
- Takes 1 to 3 days  
- Requires the availability of a tissue culture facility |
| Enzyme-linked immunosorbent assay (ELISA) | Toxin A or B | - Most common test performed  
- High specificity (92% to 98%)  
- Good sensitivity (71% to 94%)  
- Rapid (2 to 6 hrs) & inexpensive  
- Serial testing improves sensitivity |
| Latex particle agglutination | Detects the presence of glutamate dehydrogenase | - Poor sensitivity and specificity because other bacteria produce glutamate dehydrogenase  
- Rapid and inexpensive |
| Toxin culture assay/stool culture | \textit{C. difficile} | - High sensitivity  
- Low specificity. Will detect non-toxin producing bacteria.  
- Will also detect patients who are colonized with \textit{C. difficile}, but without active disease  
- Takes 3 to 4 days |
Table 3. Drug therapy for *C. difficile*.

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dosing</th>
<th>Comments</th>
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<tbody>
<tr>
<td>Metronidazole (oral)</td>
<td>- 250 mg given 4 times/day for 10 to 14 days</td>
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</tr>
<tr>
<td></td>
<td>- 500 mg given 3 times/day for 10 to 14 days</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- First line therapy</td>
<td></td>
</tr>
<tr>
<td>Metronidazole (intravenous)</td>
<td>- 500 mg every 8 hrs</td>
<td>- Reserved for NPO patients</td>
</tr>
<tr>
<td>Vancomycin (oral)</td>
<td>- 125 mg 4 times/day for 10 to 14 days</td>
<td>- Reserved for:</td>
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<tr>
<td></td>
<td></td>
<td>Metronidazole treatment failure</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pregnant patients</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Metronidazole intolerant patients</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Age &lt; 10 years</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Evidence that <em>S. aureus</em> may be causing diarrhea</td>
</tr>
</tbody>
</table>

Alternative methods of administration such as intracolonic administration must be employed for patients where delivery of active drug cannot be assured by other routes of administrations. These include patients with a small bowel obstruction, ileus, or ostomy. Metronidazole or vancomycin may be given via intracolonic administration. Table 3 lists general guidelines for drug therapy for *C. difficile*.

**Recurrent Infections**

Recurrence or relapse of diarrhea symptoms occurs in about 20% of patients following successful treatment of *C. difficile*. Recurrence can be caused by the original organism or by a new strain of the infection. The first recurrence should be treated with another 10 to 14 day course of the initial antibiotic regimen. There is no evidence to suggest that vancomycin therapy is superior to metronidazole for this purpose; therefore, above mentioned criteria should be followed. Optimal treatment for multiple recurrences/relapse has not been clearly defined. Rifampin (600 mg twice daily) in addition to vancomycin, bile acid sequestrants (e.g. cholestyramine 4 g twice daily), and prolonged treatment with metronidazole or vancomycin have all been used. The prolonged treatment regimens are usually given for about 6 weeks and include a gradual tapering of the dose of vancomycin or metronidazole.

**Prevention**

Prevention of *C. difficile* involves 3 key strategies:
- Judicious use of antibiotics
- Strict infection control practices including hand washing, isolation of infected patients, and use of gloves while treating
- Thorough cleaning/disinfection of patient care areas

**Summary**

*Clostridium difficile* infection is an important, but uncommon, cause of antibiotic-associated diarrhea. Minimization of risk factors and proper diagnosis and treatment can curtail the spread and complications of this disease.

**Anaphylactoid Reactions to Radiocontrast Media**

The intravenous administration of radiocontrast media (RCM) can cause a wide array of adverse effects with a severity ranging from minor to life threatening. The incidence of adverse events associated with RCM differs dependent upon the type of contrast agent administered. The administration of conventional, ionic, high-osmolality agents is associated with a 5 time higher frequency of adverse reactions as compared to low-osmolality, nonionic agents. Adverse events related to RCM may be classified into 3 categories: anaphylactoid, dose-dependent, or delayed. Anaphylactoid reactions may range in presentation from mild pruritus and erythema to severe hypotension, bradycardia, and bronchospasm potentially leading to death. Dose-dependent reactions include nausea, vomiting, metallic taste, generalized warmth or flushing, and development of renal failure. Delayed reactions occur ≥ 30 minutes after contrast administration, are generally consistent with flu-like symptoms, and are more common with ionic agents. The focus of this review is the prevention and management of anaphylactoid reactions associated with RCM administration.

The “allergic” response that may occur in patients receiving RCM is labeled as anaphylactoid rather than anaphylactic because IgE antibodies are not mediators of the reaction. The exact mechanism of anaphylactoid reactions is not well understood; however, these reactions may be mediated by the
release of vasoactive and inflammatory substances such as histamine, eosinophils, prostaglandins, and kinins. These reactions are unpredictable and independent of dose administered.

**Risks**
Patients at increased risk for an anaphylactoid reaction to RCM include those who have experienced such a reaction prior, and patients with a history of asthma and atopy—a genetically determined state of hypersensitivity to environmental allergens. Patients who have already experienced an anaphylactoid reaction related to RCM are of particular concern—with 16% to 44% experiencing a repeat reaction with subsequent administration. A history of an iodine allergy (i.e. shellfish) is commonly perceived to be a risk factor for development of an anaphylactoid reaction to RCM; however, documentation of this allergy is of no predictive value.

**Premedication and Choice of RCM**
Minimizing the likelihood of an anaphylactoid reaction may be accomplished by considering 2 interventions prior to treatment: pretreatment with corticosteroids and antihistamines and choice of RCM. Administration of corticosteroids prior to RCM has been shown to effectively reduce the occurrence of anaphylactoid reactions; however, premedication does not preclude an allergic reaction from occurring. Two of the most well-known corticosteroid regimens include the following:

- Prednisone – 50 mg orally 13, 7, and 1 hour prior to catheterization and
- Methylprednisolone – 32 mg orally 12 and 2 hours prior to catheterization.

The addition of diphenhydramine (usual dose 50 mg orally 1 hour prior to a procedure) to a corticosteroid reduces the risk of an anaphylactoid reaction even further. Routine administration of a H2 blocker, such as cimetidine, is not generally supported by clinical data due to the fact that anaphylactoid reactions related to RCM administration are not IgE-mediated. However, giving a H2 blocker to a patient is of low risk and is commonly done at many catheterization facilities.

For patients who present for an emergent cardiac angiography, the above dosing regimens may not be applicable. The administration of intravenous or oral corticosteroids administered too soon before RCM are likely to be ineffective at preventing anaphylactoid reactions as the lead time for the action of corticosteroids is at least 6 hours. In 1 study of 9 patients with a past anaphylactoid history requiring emergent RCM, Greenberger administered intravenous hydrocortisone 200 mg as soon as possible and every 4 hours until the completion of the study with intravenous diphenhydramine 50 mg, a one time dose 1 hour prior to the procedure. No reactions were observed to occur.

The choice of RCM also plays a role in reducing the risk of anaphylactoid reactions. The use of a nonionic, low osmolality agent has been shown to cause less “allergic” response.

Currently, the University of Illinois Medical Center formulary contains iohexol (Omnipaque®), a low-osmolality nonionic agent, iodixanol (Visipaque), an iso-osmolality, nonionic agent, and diatrizoate (Hypaque®), a high-osmolality agent. Even though low-osmolality agents are consistently associated with a reduced occurrence of anaphylactoid reactions, the significantly increased cost associated with these agents does not allow exclusive use. Generally, low-osmolality agents are reserved for patients determined to be high risk.

**Treatment**
Most severe reactions occur within the first 20 minutes of the administration of RCM; therefore, immediate response and appropriate therapy is a necessity. The treatment strategy for anaphylactoid reactions is dependent on the severity of the reaction and the specific clinical manifestation. Although treatment is not the focus of this article, therapies include fluids, epinephrine, corticosteroids, and H1 and H2 receptor antagonists. In the treatment of patients with severe anaphylactoid reactions, stabilization of the respiratory and cardiac function of the patient is the primary goal. Epinephrine may need to be administered in patients who develop bronchospasm, angioedema, or laryngeal edema.

**Conclusion**
Intravenous administration of RCM can result in a wide variety of adverse effects including anaphylactoid reactions. The “allergic” response that may occur is labeled anaphylactoid because the reaction is not IgE-mediated. Patients at increased risk for an anaphylactoid reaction include those who experienced such a reaction prior and patients with a history of asthma and atopy. Premedication with corticosteroids and antihistamines, specifically diphenhydramine, and use of a low-osmolality agent reduce the risk of anaphylactoid occurrence.
Subcutaneous Administration of Heparin and Low Molecular Weight Heparin

Heparin and low molecular weight heparin, such as enoxaparin (formulary item in the hospital) are indicated for the prevention and treatment of deep vein thrombosis, which may lead to pulmonary embolism. There have been reports of rectus muscle sheath hematomas associated with the incorrect subcutaneous administration of heparin and low molecular weight heparins such as enoxaparin. Muscle sheath hematomas have resulted in serious outcomes increasing morbidity and/or mortality.

These medications should be administered by the subcutaneous route, specifically “deep subcutaneous injection”. A correct administration technique for subcutaneous enoxaparin and heparin includes:

1. Obtain correct patient dose (to avoid the loss of drug when using the manufacturers’ prefilled syringes do not expel the air bubble from the syringe before the injection).
2. Select appropriate administration site (administration site should be alternated between the left and right anterolateral and left and right posterolateral abdominal wall – document site).
3. Deep subcutaneous injection requires “pinching an inch” of skin.
4. Insert the whole length of the needle into the skin fold created by the thumb and forefinger.
5. Hold the skin fold throughout the injection.
6. Do not rub the injection site after completion of the injection to avoid bruising.

Patients may continue low molecular weight heparin therapy after discharge. The above self-administration technique should be carefully taught and demonstrated back by the patient.

Any indicator of possible bleeding such as bruising, oozing, new abdominal or other pain, or swelling or decreased hematocrit should be communicated with the prescriber.

The follow names of low molecular weight heparins are listed for your information:

Enoxaparin (Lovenox®) – formulary
Dalteparin (Fragmin®) - non-formulary
Fondaparinux (Fondaparin®) - non-formulary

P&T Committee Formulary Action - July 2003

Additions
- Escitalopram (Lexapro): 10, 20 mg tablets
- Minoxidil (Loniten): 2.5, 10 mg tablets
- Lisinopril (Prinivil, Zestril, generics): 5, 10, 20 mg tablets

Line extensions
- Nitrofurantoin monohydrate/ nitrofurantoin macrocrystals (Macrobid): 100 mg capsules
- Didanosine EC (Videx EC): 250, 400 mg capsules

Changes in restriction
- Imipenem (Primaxin): Restricted to documented infections due to extended spectrum beta-lactamase (ESBL) producing organisms, pathogens resistant to other antimicrobial agents, and necrotizing pancreatitis

Deletions
- Phenytoin (Dilantin) injection
- Citalopram (Celexa)
- Nitrofurantoin (Macrodantin)
- Benazepril (Lotensin)

Deletion due to low use or manufacturer discontinuation
- Salmeterol (Serevent) inhalation aerosol

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