Challenges with therapy for *Clostridium difficile* infection: metronidazole vs. vancomycin

*Clostridium difficile* infection (CDI) is a common cause of hospital acquired infection (HAI) in the United States that leads to adverse events for patients (1). While metronidazole has traditionally been the agent of choice for initial treatment of CDI, management choices are no longer straight forward. Vancomycin may be more effective than metronidazole, but it is also much more expensive. This newsletter explores 1) the pros and cons of metronidazole vs. vancomycin for treatment of CDI and 2) the resources available to practitioners to provide oral vancomycin at a reasonable cost to patients.

*Oral metronidazole vs. oral vancomycin*

While vancomycin is technically the only drug that has an FDA indication for CDI treatment, both drugs have been used to treat this disease for many years. In 1995, the CDC recommended decreasing vancomycin use to reduce antibiotic pressure on enterococci; thus, metronidazole was billed as first line treatment of CDI. The emergence and widespread circulation of the NAP1 strain after 2000, however, changed the treatment paradigm. Patients with CDI treated with metronidazole had an increasing number of treatment failures and recurrences. As a result, Infectious Disease Society of America (IDSA) guidelines published in 2010 recommend more frequent use of oral vancomycin. More specifically, these guidelines recommend choosing the treatment agent based on disease severity at presentation (Table 1) and number of recurrences (2).

Table 1. IDSA guidelines for determining CDI severity

<table>
<thead>
<tr>
<th>Disease severity</th>
<th>Leukocytosis</th>
<th>Creatinine</th>
<th>Additional Clinical Features</th>
<th>Recommended Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild-moderate</td>
<td>&lt;15,000</td>
<td>&lt; 1.5 premorbid level</td>
<td></td>
<td>PO metronidazole 500mg TID</td>
</tr>
<tr>
<td>severe</td>
<td>&gt;/= 15,000</td>
<td>&gt;/= 1.5 premorbid level</td>
<td></td>
<td>PO vancomycin 125mg QID</td>
</tr>
<tr>
<td>Severe, complicated</td>
<td>&gt;/= 15,000</td>
<td>&gt;/= 1.5 premorbid level</td>
<td>Shock, ileus, hypotension, megacolon</td>
<td>PO vancomycin 500mg Q6h, IV metronidazole; +/- vancomycin retention enema if ileus present</td>
</tr>
</tbody>
</table>
These recommendations are based on small studies. For example, Zar et al conducted a prospective, double blinded randomized controlled trial involving 150 patients with CDI that showed non-inferiority of oral vancomycin compared to metronidazole for mild to moderate infection and superiority of oral vancomycin in severe disease. The patients were stratified based on disease severity for outcome analysis. Among patients with mild disease, treatment with metronidazole or vancomycin resulted in clinical cure of 90% and 98% of the patients (p =0.36). However, metronidazole resulted in clinical cure in 76% in the severe group while vancomycin resulted in clinical cure of 97% (p=0.02). Both groups had similar recurrence rates (15% in metronidazole and 14% in vancomycin) (3).

While current guidelines (2) recommend oral metronidazole as first line therapy for mild to moderate disease, many experts prefer to treat everyone with oral vancomycin for two reasons: 1) metronidazole has more gastrointestinal side effects compared to oral vancomycin, including dysguesia, nausea, and vomiting, and many people cannot tolerate a full course of the drug; and 2) the limited delivery of metronidazole to the colon. This approach makes sense given the pharmacology of the drugs. Oral metronidazole is almost completely absorbed in the small bowel and then must be secreted back into the colon. In contrast, oral vancomycin is not absorbed at all, so all of it is delivered to the colon (2, 4). In fact, many experts are predicting that metronidazole may be removed from the IDSA CDI guidelines, currently under revision. As Dr. John Bartlett once commented, “you give vancomycin to your mother and metronidazole to your mother-in-law!”

Some experts have expressed dissenting opinions on the widespread use of oral vancomycin because of its apparent increase in risk for colonization of C. difficile and other nosocomial pathogens after use. As oral vancomycin is delivered to the colon in high concentrations, other important gut flora are also impacted. Lewis et al. recently demonstrated this effect using a murine model to evaluate the effect of brief treatment with oral metronidazole and/or oral vancomycin on the susceptibility to colonization with C. difficile, vancomycin-resistant Enterococcus (VRE), carbapenem-resistant Klebsiella penumoniae (KPC), and E. coli. These researchers concluded that oral vancomycin significantly disrupted the gut microbiota compared to metronidazole and lead to higher colonization rates with C. difficile, VRE, KPC and E. coli (4).

Challenges of inpatient to outpatient oral vancomycin therapy

Clearly, treatment of CDI with oral vancomycin has advantages and disadvantages, both real and theoretical. One major disadvantage is cost. Vancomycin capsules are prohibitively expensive. Typically, hospitals can circumnavigate this issue by using IV drug compounded into an oral solution. This approach addresses the cost of inpatient treatment, but new regulations regarding oral syringe preparation may limit this practice by requiring short expiration dates and preventing batch production. Challenges also remain when patients are discharged. Using the IV formulation as an oral solution in the outpatient setting has typically required use of a compounding pharmacy and the associated limited insurance coverage and high out of pocket costs for patients. Therefore, many hospitals report routinely converting patients back to metronidazole at the time of discharge for cost reasons alone.

Thus, the conundrum is “how do patients get access to the drug they need for this condition?”

A new product may provide an alternative. The First oral vancomycin compounding kit, carries a lower daily cost (typically between $50-60 for a 150 mL bottle and approximately $100 for a 210 mL bottle). The product is stable after mixing for up to 30 days if refrigerated. More detailed information about the
product can be found at this link: http://www.cutispharma.com/products/oral-solutions-suspensions/anti-microbial/vancomycin. In our experience, local chain pharmacies can easily obtain the oral vancomycin kit, and the kit is stocked at all major pharmacy distributors.

Insurance coverage is a key consideration for outpatient therapy. The First vancomycin product carries its own NDC code and is covered by most major insurance carriers. One resource is Decision Resource Group at https://lookup.decisionresourcesgroup.com/. Here, you can quickly determine the tier categorization of a prescription based on an individual patients’ insurance coverage. This resource is web-based, includes an app that can easily be downloaded, and is free of charge.

Conclusions:

- Oral vancomycin is well tolerated and superior to oral metronidazole in cases of severe CDI
- Oral vancomycin use carries a higher theoretical risk of colonization with nosocomial pathogens and significantly disturbs gut microbiota
- The jury is still out on blanket use of oral vancomycin for CDI.
- We continue to recommend metronidazole as first line for mild disease as long as the patient tolerates therapy
- For patients with indications for oral vancomycin (ie—severe disease or metronidazole intolerance), the First oral vancomycin compounding kit is an acceptable alternative to give patients access to outpatient oral vancomycin

References:

2. Cohen SH et al. “Clinical Practice Guidelines for Clostridium difficile Infection in Adults: 2010 Update by the Society for Healthcare Epidemiology of America (SHEA) and the Infectious Diseases Society of America (IDSA)” Infection Control and Hospital Epidemiology. 2010 ; 31 : 431 -455