Hospitalizations of pediatric patients for *Clostridium difficile* infections (CDI) have doubled in the last 10 years. CDI has had a substantial impact on healthcare by causing severe disease and being difficult to treat, especially in patients with recurrent CDI.\(^1\) *C. difficile* is an anaerobic bacterium which colonizes the intestinal tract of many individuals, commonly those with prior healthcare exposure. When the microbiome is disrupted, often due to antibiotic use, *C. difficile* proliferation and toxin production occur which result in the symptoms commonly observed with CDI. Patients with CDI present with profuse, watery, bloody diarrhea. More severe cases can include fulminant colitis or toxic megacolon. Unfortunately, as many as one-fourth of pediatric patients with CDI will not respond to initial treatment and will present with episodes of recurrence. Some of these episodes of recurrence have been associated with the use of concomitant antibiotics during the treatment of the initial CDI.\(^2\)

Recurrent CDIs have a significant impact on the healthcare system due to poor therapy responses, additional use of medications, longer courses of therapy, increased costs, and increased morbidity and mortality.\(^1\) Subsequently, this has prompted hospitals to examine antibiotic use patterns and aim for the use of narrow spectrum agents and shorter courses of therapy when antibiotics are necessary.\(^3\)

All unnecessary antibiotics should be discontinued in patients presenting with an initial CDI if possible secondary to the risk of recurrence with continued use.\(^2\) The two primary treatment options for initial CDI include intravenous or oral metronidazole or oral vancomycin, depending on the severity of the presentation (Table 1). Metronidazole is almost completely systemically absorbed, and its use is complicated by adverse effects including gastrointestinal upset and metallic taste with both dosage formulations. Oral vancomycin is generally recommended in more severe cases or for patients unable to tolerate metronidazole. Oral vancomycin is not systemically absorbed and results in less systemic adverse effects.\(^3\)

<table>
<thead>
<tr>
<th>Classification</th>
<th>Primary Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild or moderate</td>
<td>Metronidazole 10 mg/kg/dose IV/PO every 8 hours (maximum single dose = 500 mg)</td>
</tr>
<tr>
<td>Severe(^a)</td>
<td>Vancomycin 10 mg/kg/dose PO QID (maximum single dose = 125 mg)</td>
</tr>
<tr>
<td>Severe, complicated</td>
<td>Vancomycin 10 mg/kg/dose PO QID (maximum single dose = 500 mg) + metronidazole 10 mg/kg/dose IV every 8 hours (maximum single dose = 500 mg) ± rectal vancomycin (if ileus present)</td>
</tr>
</tbody>
</table>

\(^a\)Leukocytosis with a white blood cell count ≥ 15,000 cells/µL or a serum creatinine ≥ 1.5 times the baseline value

Studies have demonstrated improved outcomes in patients with severe CDI treated with oral vancomycin compared to metronidazole. A meta-analysis favored the use of oral vancomycin in regards to clinical cure of CDI in both the overall and severe CDI populations (RR= 0.91, 95% CI= 0.84-0.98 and RR= 0.81, 95% CI= 0.69-0.95, respectively). However, the populations were heterogenous and the definition of clinical cure varied between studies.\(^4\) Zar and colleagues reported clinical cure in 97% and 76% of patients with severe CDI treated with oral vancomycin versus metronidazole, respectively (p=0.02).\(^4\) Both studies failed to demonstrate a significant difference between oral vancomycin and metronidazole for mild to moderate CDI despite that vancomycin is known to achieve better concentrations in the stool than metronidazole. Metronidazole concentrations are higher in watery stool specimens with a mean concentration of 9.3 mcg/g; however, once the stool becomes more formed throughout treatment, metronidazole concentrations in the stool decrease to around 1.2 mcg/g, which would not achieve adequate concentrations above the minimum inhibitory concentration (MIC) for *C. difficile*.\(^3\)

In contrast, mean vancomycin concentrations achieved in the stool during therapy range from 64 to 760 mcg/g and do not differ depending on the form of stool. Currently, guidelines recommend treatment with metronidazole for mild to moderate CDI.\(^3\) The amount of which the sub-inhibitory concentrations achieved while using metronidazole in formed stool contribute to resistance as well as undertreated CDIs and an increased risk of recurrence is unknown.
Despite appropriate initial treatment, 12 to 25% of pediatric patients will present with recurrent CDI.\textsuperscript{6} Multiple studies have looked at risk factors for recurrence in pediatric patients. A retrospective review by Kociolek and colleagues examined risk factors associated with recurrent CDI occurring within eight weeks of initial treatment. Fourteen percent of the study population developed recurrent CDI with risk factors including malignancy and tracheostomy dependence linked to recurrence.\textsuperscript{8} Malignancy and immunosuppressant use are consistently associated with recurrent CDI in the literature.\textsuperscript{2} This is likely due to the frequent use of antibiotics, hospital admissions, and chemotherapy regimens which are damaging to the intestinal microbiome in this population. Tschudin-Sutter and colleagues identified community-associated CDI and concomitant use of systemic antibiotics during the treatment of the initial CDI as risk factors for recurrent infection, which is evidence to support the discontinuation of unnecessary antibiotics during CDI.\textsuperscript{2} Additional risk factors reported in the literature include recent surgeries and number of antibiotic exposures.\textsuperscript{1}

Several studies have examined the impact of using oral vancomycin versus metronidazole for the treatment of an initial CDI and the risk of recurrence. Stevens and colleagues conducted a retrospective review using the Veteran Affairs database which examined the effects of oral vancomycin on mortality and CDI recurrence compared with metronidazole in patients presenting with an initial CDI. Two-thousand and sixty-eight patients (mean age = 68.8 years) were treated with oral vancomycin and were matched by propensity score with patients treated with metronidazole. The patients were divided into cohorts by severity (overall, mild-moderate, and severe). Patients with severe CDI who were treated with vancomycin had a lower risk of all-cause mortality compared with patients treated with metronidazole. This data likely influenced the reduction in all-cause mortality observed in patients treated with vancomycin overall. No difference was observed in rate of recurrent CDI between the oral vancomycin and the metronidazole treated patients overall and across any severity cohort (Table 2). A limitation of the study was that the diagnosis of CDI and recurrent CDI was based on a positive laboratory test result for \textit{C. difficile} and did not include any presenting symptoms (i.e. diarrhea).\textsuperscript{7} The diagnosis of CDI and interpretation in literature is difficult, especially in pediatrics, due to the potential for colonization versus an acute infection. Additional studies have also demonstrated that while oral vancomycin is a better option for patients with severe CDI, no difference in CDI recurrence has been observed between oral vancomycin and metronidazole use.\textsuperscript{4,5}

### Table 2. Relative risk (RR) of recurrence and mortality for patients treated with oral vancomycin compared with metronidazole

<table>
<thead>
<tr>
<th>Classification of CDI</th>
<th>Recurrence, RR (95% CI)</th>
<th>30-day Mortality, RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>0.98 (0.87 to 1.10)</td>
<td>0.86 (0.74 to 0.98)</td>
</tr>
<tr>
<td>Mild to moderate</td>
<td>1.07 (0.93 to 1.15)</td>
<td>0.91 (0.72 to 1.14)</td>
</tr>
<tr>
<td>Severe</td>
<td>0.96 (0.76 to 1.23)</td>
<td>0.79 (0.65 to 0.97)</td>
</tr>
</tbody>
</table>

The treatment of recurrent CDI is difficult because patients can be unresponsive to standard medication therapies. There is limited data in pediatrics and data in adults is conflicting surrounding the efficacy of oral vancomycin versus metronidazole for the treatment of the first recurrence of \textit{C. difficile}. Pépin and colleagues found that vancomycin was not associated with a lower risk of second recurrence compared with metronidazole (HR= 0.83, 95% CI= 0.5 to 1.37). Although not significant, patients treated with metronidazole for the first recurrence were more likely to have complications (i.e. shock, toxic megacolon, death). Older age and a high leukocyte count or serum creatinine were also associated with complications, which can again indicate that vancomycin is the more preferred treatment for severe infections.\textsuperscript{8} The current recommendation for the first recurrent CDI is to treat with the same medication used during the initial infection. Beyond the first recurrence, patients should be treated with oral vancomycin due to the risk of neurotoxicity with prolonged use of metronidazole.\textsuperscript{3}

Additional options need to be considered in patients who present with multiple episodes of recurrent CDI despite treatment with primary medications. Options for recurrences after treatment with oral vancomycin including use of a vancomycin taper, treatment with an alternative agent including fidaxomicin, or fecal microbiota transplantation (FMT). A vancomycin taper typically includes a dose schedule of 10 mg/kg/dose (max 125 mg/dose) PO 4 times daily for 10 to 14 days, then twice daily for 7 days, then once daily for 7 days, then every 2 to 3 days for 2 to 8 weeks. Fecal transplant involves the replacement of the damaged fecal microbiome with healthy donor stool resulting in establishment of a healthy microbiome, eradication of \textit{C. difficile}, and the resolution of symptoms. Multiple case reports and series in pediatric patients have demonstrated its safety and efficacy. FMT is currently available at Children’s Hospital Colorado through the Fecal Microbiota Transplantation Program which began in 2015 within the Digestive Health Institute.\textsuperscript{9} At CHCO, FMT is administered in the ambulatory setting using stool from a donor stool bank administered via an intragastric route. Our FMT success rate to date for the treatment of recurrent CDI has been 94% for healthy children, 75% for medically complex children, and 54% for children with underlying inflammatory bowel disease.
CDI, especially recurrent infections, have a substantial impact on morbidity and cost in the healthcare system. The use of oral vancomycin versus metronidazole for an initial infection has not been found to reduce the risk of recurrence, although positive outcomes have been associated with the use of oral vancomycin for more severe CDI. In addition, no differences in regards to subsequent CDI have been observed between the use of vancomycin versus metronidazole for treatment of the first recurrent CDI. Additional options are available for patients with refractory CDI, including fecal transplant. Practitioners can reduce patients’ risk of CDI and potentially recurrent CDI by discontinuing unnecessary antibiotics, treating with narrow-spectrum agents, and using shorter durations of therapy.

REFERENCES:

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