Preoperative Oral Antibiotics in Colorectal Surgery Increase the Rate of Clostridium difficile Colitis

Sherry M. Wren, MD, FACS; Natasha Ahmed, MD; Ayesha Jamal, MD; Bassem Y. Safadi, MD, FACS

Hypothesis: Bowel preparation traditionally consists of cathartics, oral antibiotics, and intravenous antibiotics. We hypothesize that the use of oral antibiotics in bowel preparation results in a higher rate of postoperative Clostridium difficile colitis.


Setting: Tertiary care veterans administration hospital.

Patients: Records of patients who underwent elective colorectal surgery (n = 304) were reviewed. Patients with bowel obstruction or emergent operation were excluded.

Main Outcome Measure: Detection of C difficile toxin A/B by enzyme-linked immunosorbent assay in a stool specimen within 30 days of surgery.

Results: All 304 patients received both cathartics and intravenous antibiotics. Of 304 patients, 107 (35.1%) received oral antibiotics. The rate of postoperative C difficile colitis was 4.2% in the entire study population. The rate of C difficile infection was higher in patients who received oral antibiotics (7.4%) compared with patients who did not receive oral antibiotics (2.6%; P = .03). There were no C difficile–related mortalities.

Conclusion: Oral nonabsorbable antibiotics in bowel preparation resulted in a higher rate of C difficile infection. This may be due to the additional effect of oral antibiotics on normal bowel flora. We recommend that oral nonabsorbable antibiotics not be used in preoperative bowel preparation regimens since postoperative C difficile infection can lead to additional morbidity, length of stay, and hospital costs.

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or without anastomosis or colostomy formation or takedown. Cases were also excluded if there was a diagnosis of *C. difficile* infection 30 days prior to surgery or if the patient had a preoperative bowel obstruction and could not undergo bowel preparation. Patients were only included if their postsurgical survival and follow-up were greater than 30 days. After the exclusions, there were a total of 304 patients’ records available for analysis. The medical records were examined to determine the specific preoperative bowel preparation regimen given. The type of cathartic agent, preoperative oral nonabsorbable antibiotics, and IV antibiotics were recorded for each subject. Laboratory records were then reviewed for the 30-day period following the surgery date for any stool specimens positive for *C. difficile* toxin A/B as detected by enzyme-linked immunosorbent assay. Wound infections at the time of discharge were also recorded. Data were then analyzed for statistically significant differences using $\chi^2$ analysis, Fisher exact test; $P$ values are reported at the 95% confidence interval.

### RESULTS

There were a total of 304 patients in the 78-month study period: 13 women and 291 men. Operations including colon and/or rectal resections comprised 258 cases (84.9%) and operations for colostomy creation or takedown comprised 46 cases (15.1%). Thirty patients (9.9%) had a preexisting diagnosis of spinal cord injury.

#### BOWEL PREPARATION

All 304 patients underwent bowel preparation on the day preceding surgery. All of the patients received 1 of the following cathartics: GoLYTELY (Braintree Laboratories Inc, Braintree, Mass.), Citrate of Magnesia (Aaron Industries Inc, Clinton, SC), or Fleet Phospho-soda (C. B. Fleet Co Inc, Lynchburg, Va). A total of 107 patients (35.2%) received 3 doses of 1 g each of oral neomycin and erythromycin base, and the remaining 197 patients (57.9%) received no oral antibiotics. All 304 patients received a dose of prophylactic IV antibiotic(s). Intravenous antibiotic prophylaxis regimens primarily consisted of first-generation cephalosporin in combination with metronidazole (180 patients [59.2%]), second-generation cephalosporin (64 patients [21.0%]), fluoroquinolone in combination with metronidazole or clindamycin (29 patients [9.5%]), first-generation cephalosporin alone (12 patients [3.9%]), or extended-spectrum penicillin (11 patients [3.6%]). A total of 97 patients (31.9%) received IV antibiotic regimens that did not contain metronidazole, and the remaining 207 patients (68.1%) received IV metronidazole for prophylaxis.

### C. DIFFICILE INFECTION

A total of 13 patients (4.3%) showed laboratory evidence of *C. difficile* infection in the 30 days following surgery (Table 1). There were no observed clusters of infection in the distribution of cases. Two of the patients with *C. difficile* infection (15.4%) also had a diagnosis of spinal cord injury, but when all of the patients with spinal cord injuries were analyzed, only 2 (6.7%) of 30 had a postoperative *C. difficile* infection. This is an important variable in our patient population since those patients have had frequent exposures to multiple antibiotics. Overall, 3 (21.0%) of the 13 patients with *C. difficile* infection required transfer to the intensive care unit owing to the severity of the infection. All of the patients were treated with antibiotics (metronidazole and/or oral vancomycin). No patient required further surgical treatment for the infection and there were no *C. difficile*–related mortalities.

There was a statistically significant difference in the incidence of CDC between patients who received oral antibiotics vs those who did not receive oral drug treatment (Table 2). A total of 107 patients received oral antibiotics, 8 (7.4%) of whom had postoperative *C. difficile* infection compared with 197 patients who did not receive oral antibiotics and only 5 (2.6%) of whom had postoperative *C. difficile* infection ($P = .03$). There were no significant differences for the variable of cathartic type. There was also no significant difference when the population

**Table 1. Characteristics of Patients With Postoperative *Clostridium difficile* Infection**

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Cathartic Agent</th>
<th>IV Antibiotics</th>
<th>Oral Antibiotics</th>
<th>Procedure</th>
<th>Date of Procedure</th>
<th>SCI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>GoLYTELY*</td>
<td>Second ceph</td>
<td>Yes</td>
<td>Colostomy</td>
<td>2/12/1997</td>
<td>Yes</td>
</tr>
<tr>
<td>2</td>
<td>Fleet Phospho-Soda†</td>
<td>Second ceph</td>
<td>Yes</td>
<td>Right colectomy</td>
<td>6/4/1997</td>
<td>No</td>
</tr>
<tr>
<td>3</td>
<td>Fleet Phospho-soda</td>
<td>Second ceph</td>
<td>Yes</td>
<td>Right colectomy</td>
<td>10/21/1997</td>
<td>No</td>
</tr>
<tr>
<td>4</td>
<td>GoLYTELY</td>
<td>Second ceph</td>
<td>Yes</td>
<td>Right colectomy</td>
<td>3/17/1998</td>
<td>Yes</td>
</tr>
<tr>
<td>5</td>
<td>Fleet Phospho-soda</td>
<td>First ceph</td>
<td>Yes</td>
<td>Sigmoid colectomy</td>
<td>6/17/1998</td>
<td>No</td>
</tr>
<tr>
<td>6</td>
<td>Fleet Phospho-soda</td>
<td>First ceph/metro</td>
<td>Yes</td>
<td>Sigmoid colectomy</td>
<td>4/21/1999</td>
<td>No</td>
</tr>
<tr>
<td>7</td>
<td>Fleet Phospho-soda</td>
<td>First ceph/metro</td>
<td>Yes</td>
<td>Subtotal colectomy</td>
<td>10/19/1999</td>
<td>No</td>
</tr>
<tr>
<td>8</td>
<td>Fleet Phospho-soda</td>
<td>First ceph/metro</td>
<td>Yes</td>
<td>Low anterior resection</td>
<td>2/20/2000</td>
<td>No</td>
</tr>
<tr>
<td>10</td>
<td>Fleet Phospho-soda</td>
<td>First ceph/metro</td>
<td>No</td>
<td>Low anterior resection</td>
<td>6/27/2001</td>
<td>No</td>
</tr>
<tr>
<td>11</td>
<td>Fleet Phospho-soda</td>
<td>First ceph/metro</td>
<td>No</td>
<td>Colostomy takedown</td>
<td>7/11/2001</td>
<td>No</td>
</tr>
<tr>
<td>12</td>
<td>GoLYTELY</td>
<td>Fluoro/metro</td>
<td>No</td>
<td>Sigmoid colectomy</td>
<td>1/30/2002</td>
<td>No</td>
</tr>
<tr>
<td>13</td>
<td>Fleet Phospho-soda</td>
<td>First ceph/metro</td>
<td>No</td>
<td>Right colectomy</td>
<td>12/18/2002</td>
<td>No</td>
</tr>
</tbody>
</table>

Abbreviations: ceph, cephalosporin; first ceph, first-generation cephalosporin; fluoro, fluoroquinolone; IV, intravenous; metro, metronidazole; SCI, spinal cord injury; second ceph, second-generation cephalosporin.

*GoLYTELY (Braintree Laboratories Inc, Braintree, Mass).*
†Fleet Phospho-soda (C. B. Fleet Co Inc, Lynchburg, Va).
was analyzed based on the use of IV metronidazole (Table 2). Overall, the wound infection rate was 13.8% (42/304). Patients who received oral antibiotics had a 14.9% incidence of CDC compared with 13.2% in those patients who did not receive oral antibiotics. This difference was not statistically different ($P = .20$).

**Table 2. Comparison of Clostridium difficile Colitis Incidence Effect of Oral Antibiotics and Intravenous Metronidazole**

<table>
<thead>
<tr>
<th></th>
<th>C difficile Positive, No.</th>
<th>C difficile Negative, No.</th>
<th>Incidence, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral antibiotics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>8</td>
<td>99</td>
<td>7.4</td>
</tr>
<tr>
<td>No</td>
<td>5</td>
<td>192</td>
<td>2.6†</td>
</tr>
<tr>
<td>Intravenous metronidazole</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>8</td>
<td>199</td>
<td>3.9†</td>
</tr>
<tr>
<td>No</td>
<td>5</td>
<td>92</td>
<td>5.1</td>
</tr>
</tbody>
</table>

* $P = .03$  
† $P = .20$ (nonsignificant).

The introduction of preoperative bowel preparation was considered a major advancement in elective colon and rectal surgery. The underlying principle was the reduction of intraoperative bacterial contamination by diminishing colonic bacterial counts using a combination of mechanical cleansing and oral antibiotics. In the 1970s, randomized controlled clinical trials demonstrated that administering cathartics and neomycin-erythromycin base reduced the rate of postoperative infectious complications in elective colorectal surgery.⁴ The proven efficacy of this approach led to the widespread adoption of the Nicholls-Condon preparation, which is still in use today. In 1997, Nichols et al⁵ surveyed 471 colorectal surgeons in North America and found that the majority (86.5%) of them were using a combination of oral and IV antibiotics preoperatively. Only 11.5% of the surgeons surveyed used IV antibiotics without oral antibiotics.

Recently, the role of mechanical bowel preparation in lowering postoperative infectious complications has been put to question by several randomized controlled clinical trials.⁶ On the other hand, the utility of prophylactic antibiotics has been established without a doubt. The choice of antibiotics is debated, namely, whether antibiotics should be given orally, intravenously, or in combination.⁷⁸ The comparative data are vague and subject to many variables, including many types of antibiotics used. There are sufficient data to suggest that the use of IV antibiotics is effective prophylaxis and that the use of oral antibiotics may not offer additional advantages.⁸ This has become more relevant because oral antibiotics are given the day before surgery but most patients are now admitted on the same day of their scheduled elective procedures and may not be receiving mechanical bowel preparation.⁵¹¹

Most studies comparing the different preoperative antibiotic regimens have looked at postoperative wound infections, anastomotic leaks, and septic complications as end points.⁵⁹ Adverse effects and complications directly related to antibiotic use, such as CDC, are rarely reported. In fact, there are very few data on the rate of CDC complicating colorectal procedures. In a prospective study of 374 surgical patients, the rate of symptomatic CDC (defined as >3 bowel movements per 24 hours and being cytotoxin or culture positive) was 5.6%.¹ In the subgroup of patients who underwent colectomy, the rate was 21.0%. The highest rate of C difficile infections (29.0%) was in patients who underwent an operation for small- or large-bowel obstruction. There are several factors that increase the risk of CDC following colon and rectal operations. Many patients who undergo these procedures are elderly with underlying infections or malignancy and may have altered host immune responses. Perhaps the most important risk factor is the administration of antibiotics in the perioperative period. Both oral and IV antibiotics change the colonic microflora and predispose patients to the development of C difficile infections.⁴⁵¹²

The purpose of our study was to determine the rate of CDC following elective colorectal procedures at our institution, specifically by looking at the effect of the preoperative antibiotic regimen used. During the time period of the study (1997-2003), we gradually shifted from using a combination of oral and IV antibiotics to only IV antibiotics. To compare the 2 groups and minimize selection bias, we excluded patients who were unable to receive mechanical bowel preparation and hence would have been unable to receive oral antibiotics. This eliminated patients who underwent emergent operations for any cause and those who had total bowel obstructions. We also excluded patients who had a diagnosis of C difficile infection 30 days prior to surgery. The study results demonstrate a higher rate of CDC observed in the group of patients who received oral and IV antibiotics vs those who received IV antibiotics only (7.4% vs 2.6%, respectively; $P = .03$). The wound infection rates were similar in both groups.

As in all retrospective studies, there are several limitations in this study. *Clostridium difficile* infection was defined by a positive cytotoxin A/B assay within 30 days of surgery. These assays were not performed routinely; rather, they were only performed when colitis was clinically suspected. Therefore, some cases of C difficile infection could have been missed if they were diagnosed endoscopically or treated empirically. Our facility does not perform C difficile cultures, so patients who may have been toxin negative but culture positive would not be identified. The trend in eliminating oral antibiotics occurred over time; therefore, we wanted to be sure that the noted differences were not related to a cluster effect. None of the observed C difficile infections occurred in the same calendar month and year.

We hypothesize that the difference in the CDC rate noted among the 2 groups is related to the greater impact of oral antibiotics on colonic microflora. In a rat model, neomycin-erythromycin was shown to be more effective than intramuscular cefoxitin in reducing both intraluminal and mucosal surface-associated colonic microflora.¹² Another possible explanation for our finding could be related to the specific IV antibiotic used. In a
prospective randomized trial comparing an oral combination of neomycin and erythromycin base with an oral combination of neomycin and metronidazole, there was a lower rate of positive C difficile stool samples in the metronidazole group (2.5% vs 11.9%, respectively). The difference was not statistically significant but suggested that metronidazole might have a protective effect in reducing C difficile colonization.13 In our study, we found no significant difference in the incidence of CDC based on whether IV metronidazole was used.

Colorectal cancer is the second most common type of cancer in the United States, with more than 150,000 newly diagnosed cases per year.14 The indications for colorectal cancer may be related to oral antibiotic usage. Dr Wren and colleagues commented that antibiotic therapy may have limited benefit in the standard therapy that may have limited benefit in the

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References


Discussion

Mark L. Welton, MD, Stanford, Calif: Drs Wren and Safadi retrospectively reviewed 304 patients undergoing elective colectomy at a veterans hospital over a 78-month period of time in an effort to determine whether the standard nonabsorbable oral antibiotic preparation is of benefit when combined with intravenous antibiotics. As they note, it has long been the standard of care to require cathartic bowel preparation in combination with an oral antibiotic preparation. These recommendations were made initially in 1971 by Nichols and Condon, who cited historical evidence to prove the mechanical bowel preparation was mandatory. Subsequent trials until the 1990s focused on types of bowel preparation, for example, mannitol, PEG (polyethylene glycol), saline, Fleet's Phospho-soda, inpatient vs outpatient bowel preparation, and choices of antibiotic therapy, and types of delivery, ie, first-generation, second-generation, third-generation cephalosporins or intravenous, oral, or intraperitoneal delivery of the antibiotics. In the early 1990s, a few trials began to focus on the importance of mechanical bowel preparation and, as Dr Wren just noted, in 2003, a Cochrane Analysis reported that there is no data to support mechanical bowel preparation. Indeed, it may in fact be harmful. This study details potential complications directly related to oral antibiotic usage. Dr Wren and colleagues found that Clostridium difficile colitis was more common in patients who received nonabsorbable antibiotics and intravenous antibiotics than those patients who received only parenteral antibiotic therapy. Overall, the authors found a postoperative Clostridium difficile infection rate of 4.3%. However, there was a significant difference between the 2 groups, 7.4% vs 2.6% in the oral and intravenous antibiotic group and intravenous antibiotics only group, respectively. Importantly, the wound infection rates were essentially the same, with a rate of 13.8% overall, and rates of 14.9% vs 13.2% for those that received oral and intravenous antibiotics vs those that received intravenous antibiotics alone, respectively.

Although this study is retrospective and has the associated limitations, I believe the authors raise a valid concern regarding the standard therapy that may have limited benefit in the
era of improved intravenous antibiotic coverage. These data would suggest that we abandon the use of oral antibiotics because the wound infection rates are the same and the complication of \textit{Clostridium difficile} colitis is statistically significantly increased when oral antibiotics are given.

As the authors note, they may have underestimated the actual rate of \textit{Clostridium difficile} colitis in that they only studied symptomatic patients, and the stool culture test is not as sensitive as the \textit{C difficile} toxin assay. However, it does not seem likely that this would favor one group over the other. They do have somewhat limited follow-up at 30 days, and \textit{C difficile} colitis may occur up to 6 to 8 months afterwards, but again, both groups would seem to be at equal risk for a late presentation.

I have a few questions for the authors. I noticed that in the first 2 years of the studies, the patients received a second-generation cephalosporin after which the authors changed to a first-generation cephalosporin and metronidazole or other combinations. Why was this change in practice instituted? How were the antibiotic choices made? Was this attending preference, in- combinations. Why was this change in practice instituted? How were the antibiotic choices made? Was this attending preference, in- combinations. Why was this change in practice instituted? How were the antibiotic choices made? Was this attending preference, in-

Practice recommendations for intravenous antibiotics suggest 1 dose of perioperative antibiotics 30 minutes prior to skin incision and no postoperative antibiotics. I know that, frequently, patients receive postoperative antibiotics despite our best efforts. You state clearly that the patients received 1 dose preoperatively. Do you know whether some patients received postoperative antibiotics despite your best intentions and whether these patients may have had an increased incidence of \textit{C difficile} colitis?

Given the retrospective nature of the study and the gradual shifting of your practices at the Palo Alto VA [Veterans Affairs] Hospital, do you think it is possible that there was an increased awareness of \textit{C difficile} colitis and the modes of transmission of the agent and that this coincided with your decreased infection rate and was, rather, the cause rather than simply your antibiotic changes?

The authors seem to suggest that they anticipated a beneficial effect from the use of intravenous metronidazole, but this was not seen. Could you please comment on why you anticipated such a potential benefit? As you are aware and you stated in your presentation, metronidazole has been reported to cause \textit{C difficile} colitis.

Finally, what motivated the authors to phase out their usage of oral antibiotics as part of their preoperative bowel preparation? I find no fault with that and have personally eliminated it in my practice because of the side effects; it is very poorly tolerated and the patients often develop nausea and vomiting the night before surgery, worsening the dehydration one might see with their bowel preparation.

\textbf{J. Dennis Baker, MD, Los Angeles, Calif:} Did you try to get a handle on whether the preoperative intravenous antibiotics were given in a timely fashion? This issue remains a problem at many hospitals.

\textbf{Fred A. Weaver, MD, Los Angeles:} I don't remember exactly how many years ago, 20 or 30, this whole colonic prep