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.

**Design:** Retrospective case-controlled study of elective colon surgery patients; January 1997 to June 2003.

**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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*Clostridium difficile* colitis (CDC) is a known complication of colon and rectal surgery occurring in up to 21% of patients. Several contributing factors, including advanced age, immune dysfunction, and intestinal stasis, are implicated. More importantly, mechanical bowel preparation and antibiotics alter the normal enteric flora and increase the risk of *C difficile* colonization and colitis. *Clostridium difficile* colitis can increase perioperative morbidity and mortality, leading to increased hospital stay, drug costs, and further surgical care. Prophylactic antibiotics have become standard in elective colon and rectal surgery, but controversy persists on the ideal choice and route of antibiotics: oral, intravenous (IV), or both in combination. Most studies comparing these regimens have looked at postoperative wound and septic complications as end points and have not addressed complications related to antibiotic use, such as CDC. It is well known that both mechanical cathartic agents and oral antibiotics diminish the intraluminal bacterial counts, thereby predisposing patients to *C difficile* colonization. The purpose of this study was to determine the rate of CDC following elective colon and rectal surgery with or without the administration of preoperative oral antibiotics in the bowel preparation regimen. We hypothesized that the use of oral antibiotics in bowel preparation would result in a higher rate of postoperative CDC owing to the additive effect on the native bowel flora.

**METHODS**

The patients for this retrospective case study were identified by operating room database case log reports. All patients undergoing open or laparoscopic colon or rectal surgery from January 1997 to June 2003 were selected. Cases were excluded from the analysis if the procedure was listed as a transanal excision, total proctocolectomy, or emergency operation. Medical records of the remaining patients were closely reviewed to include only those patients who received preoperative bowel preparation for elective operations, including resections with...
or without anastomosis or colostomy formation or takedown. Cases were also excluded if there was a diagnosis of \textit{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 postoperative 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 \textit{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: GoLYTLEY (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 cefalosporin in combination with metronidazole (180 patients [59.2%]), second-generation cefalosporin (64 patients [21.0%]), fluoroquinolone in combination with metronidazole or clindamycin (29 patients [9.5%]), first-generation cefalosporin 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 \textit{C. difficile} infection in the 30 days following surgery (\textbf{Table 1}). There were no observed clusters of infection in the distribution of cases. Two of the patients with \textit{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 \textit{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 \textit{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 \textit{C. difficile}–related mortalities.

### Table 1. Characteristics of Patients With Postoperative \textit{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>GoLYTLEY*</td>
<td>Second ceph</td>
<td>Yes</td>
<td>Colostromy</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 colostromy</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 colostromy</td>
<td>10/21/1997</td>
<td>No</td>
</tr>
<tr>
<td>4</td>
<td>GoLYTLEY</td>
<td>Second ceph</td>
<td>Yes</td>
<td>Right colostromy</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 colostromy</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 colostromy</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 colostromy</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>2/9/2000</td>
<td>No</td>
</tr>
<tr>
<td>9</td>
<td>Fleet Phospho-soda</td>
<td>First ceph/metro</td>
<td>No</td>
<td>Sigmoid colostromy</td>
<td>3/1/2000</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>Colostromy takedown</td>
<td>7/11/2001</td>
<td>No</td>
</tr>
<tr>
<td>12</td>
<td>GoLYTLEY</td>
<td>Fluoro/metro</td>
<td>No</td>
<td>Sigmoid colostromy</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 colostromy</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 cefalosporin.

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>Oral antibiotics</th>
<th>Positive, No.</th>
<th>Negative, No.</th>
<th>Incidence, %</th>
</tr>
</thead>
<tbody>
<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>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. The proven efficacy of this approach led to the widespread adoption of the Nichols-Condon preparation, which is still in use today. In 1997, Nichols et al 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. 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. 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. 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.

Most studies comparing the different preoperative antibiotic regimens have looked at postoperative wound infections, anastomotic leaks, and septic complications as end points. 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%. 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.

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. 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 *Clostridium 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. 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. The indications for colorectal resection besides cancer include other common conditions such as neoplastic polyps and diverticular disease. The incidence of CDC complicating colectomy is not well documented but has been reported as being as high as 21.0%. Interestingly, in this study the observed *C difficile* infection rate was only 4.2%. Even with this lower overall rate, this complication is not to be minimized. Three of the 13 patients with CDC required transfer to an intensive care unit owing to the severity of the colitis, and all patients with CDC had increased hospital stays. Fortunately, most cases of CDC are effectively treated and have no long-term sequelae. However, some cases progress to fulminant colitis and even death, and at a minimum, many lead to prolonged hospital stay and disability. This infection is a fairly common occurrence and efforts to minimize it should be explored. To our knowledge, there have been little data regarding the effect of a specific bowel preparation regimen on the risk of CDC. Most studies have focused on the wound infections and septic complications. This study is retrospective in nature and, as such, cannot conclusively prove the underlying hypothesis that oral antibiotics lead to an increased risk of CDC. The entire role of bowel preparation and its components is currently being redefined. We would suggest that prospective trials in the future not only track the development of *C difficile* infections but also question the role of oral antibiotics.

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Correspondence: Sherry M. Wren, MD, Department of Surgery, Stanford University School of Medicine, G112 PAVAHCS, 3801 Miranda Ave, Palo Alto, CA 94304 (swren@stanford.edu).

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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 early 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 *Clostridium difficile* colitis is statistically significantly increased when oral antibiotics are given.

As the authors note, they may have underestimated the actual rate of *Clostridium difficile* colitis in that they only studied symptomatic patients, and the stool culture test is not as sensitive as the *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 *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 antibiotic changes made? Was this attending preference, institutional policy, or simply resident choice? What was the rate of antibiotic choices made? Was this attending preference, institutional policy, or simply resident choice? What was the rate of *C. difficile* colitis in those first 2 years versus the last 4 years after the antibiotic change?

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 *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 *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 *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.

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.

Fred A. Weaver, MD, Los Angeles: I don't remember exactly how many years ago, 20 or 30, this whole colonic prep [preparation] started, and then incrementally the prep has been deleted and now we are right back to no prep. So is it the improvement in the antibiotics that are now available that has changed this, or is there something that we are missing more fundamental that has changed?

Dr Wren: I would like to thank Dr Welton for his kind comments. The gradual change of intravenous antibiotic prophylaxis was based on some adverse experiences; we had a number of patients with postoperative bleeds from minor things such as nasogastric tube trauma attributed to significant INR [international normalized ratio] elevation, an adverse drug reaction well known with certain second-generation cephalosporins. Next, we standardized antibiotic choices based on attending surgeon consensus, which was typically to give standard prophylaxis with a first-generation cephalosporin with metronidazole unless there was a penicillin allergy. To answer your second question about the specific incidence of CDC in the early and later time periods: the rate of *C. difficile* colitis in the first 2 years was 5.3%. Seven patients had colitis during that time, 4 of which had received a second-generation cephalosporin for prophylaxis. In the subsequent 4-year period, 6 patients had *C. difficile* colitis for a rate of 3.5%; none of those patients had received second-generation cephalosporins, even though 7% of all the patients in that time period were still getting that drug for prophylaxis.

Your third question was about postoperative antibiotics. A small number of our patients did receive postoperative antibiotics whether we wished them to or not. We did not analyze those patients separately.

As to your last 2 questions, the motivation to stop oral antibiotics was based on personal perception that we seemed to have a high rate of colitis post colon and rectal procedures. We then based our decision to eliminate the oral antibiotics on the literature which supported the lack of their efficacy. At a time when we went to the new computerized physician order entry package, we standardized our bowel preparation regimen available as a choice on the computer based on a consensus agreement to eliminate the oral antibiotics. An additional bonus outlined by Dr Welton was that we no longer received patient complaints about having to take the unpleasant oral agents. There was no other institutional awareness or policy change concerning CDC [*C. difficile* colitis] that I know of to account for the observed decrease in incidence.

Your question about metronidazole is based on some animal data that suggested that oral metronidazole in bowel preparation resulted in a lower incidence of *C. difficile* colitis. Intravenous antibiotics were most often given in the OR [operating room] prior to induction; we are able to verify that from the anesthetic records.

Dr Weaver, regarding the issue of the role of bowel preparation, I agree it is very confusing. We may be moving toward a time where we are going to abandon mechanical prep. The negative effects of bowel preparation may be from the prep's effect on host factors and the loss of normal colonic flora. The mechanism is not known at this time. Clearly, prophylactic preoperative intravenous antibiotics are going to remain. Only a randomized prospective trial is going to answer this question convincingly and we can all await that data.