Preoperative Antibiotic Colon Preparation: Have We Had the Answer All Along?

Matthew D Zelhart, MD, Adam T Hauch, MD, Douglas P Slakey, MD, MPH, FACS, Ronald L Nichols, MD, FACS

The high rate of infection-related complications in colorectal surgery has a considerable impact on morbidity, mortality, and cost. Given the increasing emphasis on cost effectiveness and quality outcomes, minimizing infectious postoperative complications will influence physician credentialing and reimbursement in the future.

The evolution of bowel preparations before elective colorectal surgery spans at least 60 years. Decades of research on lowering the surgical infection rate have led to a variety of pre- and perioperative antibiotic recommendations and practices. Sixty years ago, mechanical preparation alone was used, which was followed by the addition of different oral antibiotics. Then IV antibiotics, in addition to oral, were introduced, eventually leading to IV antibiotics alone being recommended. To date, there is no consensus on best practice and therefore no standard to follow.

To better understand the myriad of options available, this article reviews the history and evolution of antibiotic prophylactic bowel preparation for colorectal surgery to elucidate recommendations for surgeons.

EVOLUTION OF APPROACHES TO PREOPERATIVE BOWEL PREPARATION

1950s to 1960s
In 1956, Cohn and colleagues found that oral neomycin and nystatin were effective in decreasing aerobic colonic bacteria in healthy humans. In 1957, study of colon resections in dogs demonstrated that oral antibiotics improved survival and decreased anastomotic leaks.

Early 1970s
Beginning in the early 1970s, Nichols and Condon demonstrated that oral antibiotics improved survival and decreased anastomotic leaks.

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major anastomotic leak, fecal septicemia, or death due to sepsis, between the 2 groups, with a 43% infectious complication rate in the placebo group compared with 9% in the NE group (p < 0.0002). The rate of surgical site infections was also significantly different between groups (35% placebo vs 9% NE; p < 0.002) (Table 1). In rectal resections, they also showed a 40% infection rate in the placebo group and a 0% infection rate in the NE group. The authors noted that there was no increase in diarrhea, colitis, or emergence of resistant organisms.23

The next 2 VA cooperative studies were published in 1978 and 1983 by Condon and colleagues16,17 in an attempt to determine the effectiveness of parenteral antibiotic prophylaxis compared with the established oral NE regimen (Table 1). These prospective double-blinded studies were performed in 16 VA hospitals and included 193 and 1,128 patients, respectively. In the first study, IV cephalothin alone was the parenteral arm of the study. All patients still received a mechanical bowel preparation with magnesium citrate. The oral antibiotic arm included NE administered at 1:00 PM, 2:00 PM, and 11:00 PM the day before surgery, with or without concomitant administration of IV cephalothin. The parenteral arm was stopped after 10 months because of data demonstrating ineffectiveness of IV antibiotics alone. The overall rate of septic complications in the oral arm was 6% vs 39% in the parenteral arm (p < 0.001). Wound infection rates were also significantly different (6% NE group vs 30% parenteral group; p < 0.001).16 The second study in 1983 demonstrated that the addition of parenteral antibiotics to oral NE had no substantial effect on rates of wound infection or overall septic complications, such as intra-abdominal abscess, nonlocalized peritonitis, major anastomotic leak, fecal septicemia, or death due to sepsis.17 In this study, 1,128 patients received mechanical cleansing and the NE preparation and were then randomized to receive either IV cephalothin or placebo. The study found no significant difference in infection rate (5.7% with IV vs 7.8% with oral antibiotics alone; p = 0.22)17 (Table 1). However, in the patients having a rectal resection, the p value approached significance (p = 0.066) in favor of adding IV cephalothin.17

In 1983, Kaiser and colleagues24 conducted a prospective randomized study in which 119 patients received either IV cefoxitin only or the combination of NE and IV cefazolin. The authors showed that in operations lasting longer than 4 hours, patients with IV therapy alone had an infection rate of 37.5%, and those with combination therapy had an infection rate of 0% (p < 0.05).24 For all operations, regardless of duration, infection rates for combination therapy were 3.2% and infection rates for IV monotherapy were 12.5% (p = 0.06).

In the late 1980s, Lindsey and colleagues25 conducted studies using scanning electron microscopy and showed that oral NE was the most effective regimen for reducing both the intraluminal and mucosal surface colonic microflora. Smith and co-investigators26 later repeated a similar study in human populations demonstrating the effectiveness of oral NE, suggesting that this dual suppression of colonic microflora could be a reason for the clinical success witnessed during the previous 2 decades when using NE.

1990s
During the 1990s, there were few major studies investigating the use of antibiotics for colorectal surgery compared with the previous 2 decades.27 The studies at this time were designed to assess optimal parenteral antibiotic regimens, despite the fact that most authoritative reports endorsed the use of oral antibiotics.28-33 For example, Solla and Rothengberger28 reported in 1990 that 92% of surgeons were using oral antibiotics and Nichols and colleagues35 published a survey of 471 surgeons demonstrating that 86.5% used oral with parenteral antibiotics.

A meta-analysis performed by Song and Glenny,36 showed that oral antibiotics alone were not as effective as when combined with parenteral. In addition, Coppa and Eng37 documented increased rates of wound infection, intra-abdominal infection, and anastomotic leak to when parenteral cefoxitin was used alone compared with oral NE prophylaxis.

2000 to 2010
In 2000, Galandiuk and Mortensen noted that the advent of oral NE was a significant contribution and one of the greatest advances to the safety of colon and rectal surgery.38 Neomycin and erythromycin are not antibiotics that are commonly used to treat infections, which makes resistance less of a concern. In addition, NE have been used for decades without evidence of any major long-term side effects. Zmora and colleagues39 conducted a survey of 515 colorectal surgeons in 2003 that showed that 75% used oral antibiotics routinely and an additional 11% used them selectively.

Several studies in this era evaluated the effectiveness and necessity of mechanical bowel preparation before elective colorectal surgery. In 2007, Jung and colleagues39 published a multicenter randomized clinical trial involving 1,343 patients that concluded mechanical bowel preparation did not lower complication rates and suggested that it could be omitted before elective colonic resection. There were no significant differences between the 2 groups in infectious or cardiovascular complications. Several meta-analyses have reiterated this point.40-43
<table>
<thead>
<tr>
<th>First author</th>
<th>Year</th>
<th>n</th>
<th>First study arm</th>
<th>Second study arm</th>
<th>Mechanical bowel preparation?</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clarke</td>
<td>1977</td>
<td>116</td>
<td>Mechanical preparation with NE</td>
<td>Mechanical preparation with placebo</td>
<td>Yes</td>
<td>Sepsis rate of 43% in placebo group, 9% in NE group (p &gt; 0.0002)</td>
</tr>
<tr>
<td>Condon</td>
<td>1978</td>
<td>193</td>
<td>IV cephalothin with oral placebo</td>
<td>Oral NE with or without IV cephalothin/placebo</td>
<td>Yes</td>
<td>Overall sepsis rates of 39% vs 6% in oral NE group (p &lt; 0.001)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Wound infection rates 30% vs 6% in oral NE group (p &lt; 0.001)</td>
</tr>
<tr>
<td>Condon</td>
<td>1983</td>
<td>1,128</td>
<td>Oral NE + IV placebo</td>
<td>Oral NE + IV cephalothin</td>
<td>Yes</td>
<td>Nonsignificant lower infection rates for combination (5.7%) over oral monotherapy (7.8%) (p = 0.22)</td>
</tr>
<tr>
<td>Itani</td>
<td>2006</td>
<td>1,002</td>
<td>IV ertapenem</td>
<td>IV cefotetan</td>
<td>Yes</td>
<td>Surgical site infections 26.2% with cefotetan vs 17.1% with ertapenem Oral antibiotics not allowed in this study</td>
</tr>
<tr>
<td>Cannon</td>
<td>2012</td>
<td>9,940</td>
<td>SCIP-approved IV</td>
<td>Oral NE or oral metronidazole/neomycin + SCIP-approved IV</td>
<td>73% received prep</td>
<td>Decreased infection rates for the combination therapy (9%) over monotherapy (18.1%) (p &lt; 0.0001) In another end point, p = 0.47 for oral antibiotics vs oral antibiotics with mechanical bowel preparation</td>
</tr>
<tr>
<td>Toneva</td>
<td>2013</td>
<td>8,180</td>
<td>SCIP-approved IV</td>
<td>Oral NE or oral metronidazole/neomycin + SCIP-approved IV</td>
<td>None 17.2%; mechanical alone 39%; oral antibiotics with or without mechanical prep 43.7%</td>
<td>Lowest infection rate for combination oral and IV therapy with mechanical preparation (8.6%) vs IV monotherapy with mechanical preparation (19.5%) vs IV monotherapy without mechanical preparation (18.6%) (p &lt; 0.0001)</td>
</tr>
<tr>
<td>Deierhoi</td>
<td>2013</td>
<td>5,750</td>
<td>Combined oral (NE used in 74%) and SCIP-approved IV antibiotics</td>
<td>SCIP-approved IV antibiotics alone</td>
<td>Undefined</td>
<td>Lower surgical site infection rate with combination antibiotics (6.3%) vs IV antibiotics alone (16.7%) (p &lt; 0.0001)</td>
</tr>
</tbody>
</table>

NE, neomycin-erythromycin base; SCIP, Surgical Care Improvement Practice.22
Most articles from this time began phasing out oral antibiotics entirely as a study arm, even though the use of IV antibiotics alone resulted in higher infection rates in most studies. For example, studies were conducted comparing ertapenem and cefotetan and demonstrated that ertapenem has greater reductions in surgical site infection. Although these articles are credited with bringing IV single-drug prophylaxis into its current popularity, neither of these studies allowed the use of oral antibiotics, which prevented comparison with the prevailing standard combination therapy. It is curious that the jump to IV monotherapy commenced without clear data to support it. The infection rates in Itani and colleagues’ study were 26% for cefotetan and 17% for ertapenem, both higher than the infection rates repeatedly demonstrated for oral antibiotic regimens (<11%).

In 2009, Hayashi and Wilson commented that oral antibiotics were not allowed in either arm of the study. They demonstrated a reduced risk of wound infections (relative risk = 0.57; 95% CI, 0.43–0.76; p = 0.0002; risk difference = −0.05; 95% CI, −0.08 to −0.02; p = 0.0003) compared with participants receiving IV antibiotics only. In 2011, a literature review by Fry also concluded that oral antibiotics needed to be added to surgeons’ regimens for elective colorectal surgery.

In 2012, Cannon and colleagues published a retrospective study of 112 VA hospitals and showed that the use of oral antibiotics, with or without mechanical bowel preparation, resulted in a significant decrease in surgical site infections compared with patients without oral bowel preparation and IV antibiotics alone (9.0% vs 18.1%; p < 0.0001). Additionally, they showed total colectomy and rectal resections had higher risks of infection when compared with ileocolic resection. This group also demonstrated a decreased length of stay (p < 0.0001) and fewer 30-day readmissions for patients receiving oral antibiotic bowel preparation. Additionally, they showed that patients undergoing a total colectomy or rectal resection were at a higher risk for increased length of stay and readmission (p < 0.0001).

Deierhoi and colleagues retrospectively examined 5,750 elective colorectal procedures. This study showed that preoperative administration of combination oral and IV antibiotics resulted in a surgical site infection rate of 6.3% vs 16.7% in the group given IV antibiotics alone (p < 0.0001). Surgical site infection rates dropped for each type of IV antibiotic used when an oral antibiotic preparation was also given. For example, the infection rate was 14.5% when ertapenem was given alone, but was 4.4% when oral antibiotics were given in combination. In addition, Deierhoi and colleagues found second-generation cephalosporins to be least effective, even though they are the principally recommended antibiotics in the Surgical Care Improvement Practice guidelines. This places doubt on the importance of Itani and colleagues’ 2006 study in which IV ertapenem was deemed the antibiotic of choice, despite the fact that oral antibiotics were not allowed in either arm of the study.

Although concern exists when using combination antibiotics, such as the theoretical increase in Clostridium difficile infection, as suggested in the single-institution retrospective study by Wren and colleagues in 2005, other recent and more powerful studies, such as the multicenter study of 2,297 patients conducted by Krapohl and colleagues in 2011, showed no statistical difference in the rates of C difficile infection. Another study by

2010 and beyond

Renewed interest in oral antibiotics is exemplified by Englesbe and colleagues in their retrospective study of elective colectomies at 24 Michigan hospitals. The 36.4% of patients who received oral antibiotics (76.3% of these were NE) in addition to preoperative IV antibiotics were less likely to have surgical site infections (4.5% vs 11.8%; p = 0.0001). In 2011, Bellows and colleagues performed a meta-analysis of 16 randomized controlled trials comparing combined oral and parenteral vs IV antibiotics only. They demonstrated a reduced risk of wound infections (relative risk = 0.57; 95% CI, 0.43–0.76; p = 0.0002; risk difference = −0.05; 95% CI, −0.08 to −0.02; p = 0.0003) compared with participants receiving IV antibiotics only. In 2011, a literature review by Fry also concluded that oral antibiotics needed to be added to surgeons’ regimens for elective colorectal surgery.

Data from these studies led surgeons to conclude that oral antibiotics are effective, with or without mechanical bowel preparation. For example, Deierhoi and colleagues demonstrated a significant decrease in surgical site infections when oral antibiotics were given with IV antibiotics, as compared with patients receiving IV antibiotics alone. This group also showed a decrease in infection rates when oral antibiotics were given in combination with IV antibiotics. Additionally, they showed that patients undergoing a total colectomy or rectal resection were at a higher risk for increased length of stay and readmission (p < 0.0001).

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Table 2. Superiority of Oral and Parenteral Antibiotic Combination Therapy

<table>
<thead>
<tr>
<th>First author</th>
<th>Year</th>
<th>n</th>
<th>Monotherapy</th>
<th>Combined therapy</th>
<th>Mechanical bowel preparation?</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kaiser</td>
<td>1983</td>
<td>119</td>
<td>IV cefoxitin</td>
<td>Oral NE + IV cefazolin</td>
<td>Yes</td>
<td>Infection rate for combination therapy (3.2%) vs monotherapy (12.5%) (p = 0.06) Procedures &gt;4 hours had lower infection rates for combination therapy (0%) vs monotherapy (37.5%) (p &lt; 0.05)</td>
</tr>
<tr>
<td>Coppa</td>
<td>1988</td>
<td>350</td>
<td>IV cefoxitin</td>
<td>Oral NE + IV cefoxitin</td>
<td>Yes</td>
<td>Lower infection rates for all comers in combination group (5%) over monotherapy (11%) Procedures &gt;215 minutes showed a much lower infection rate for combination (2%) over monotherapy (19%) (p &lt; 0.05)</td>
</tr>
<tr>
<td>Stellato</td>
<td>1990</td>
<td>169</td>
<td>IV cefoxitin alone or oral NE alone</td>
<td>Oral NE + IV cefoxitin</td>
<td>Yes</td>
<td>Decreased infection rates for combination therapy (7.8%) compared with cefoxitin alone (11.7%) or NE alone (11.4%), not statistically significant</td>
</tr>
<tr>
<td>Lewis</td>
<td>2002</td>
<td>208</td>
<td>IV amikacin/metronidazole</td>
<td>Oral metronidazole/neomycin + IV amikacin/metronidazole</td>
<td>Yes</td>
<td>Surgical wound infections in (4.6%) of combination group and (16%) in monotherapy group (p &lt; 0.01)</td>
</tr>
<tr>
<td>Nelson</td>
<td>2009</td>
<td>30,880 in 182 trials</td>
<td>Meta-analysis</td>
<td>Meta-analysis</td>
<td>Undefined</td>
<td>Decreased infection rates for combination therapy compared with IV monotherapy (RR = 0.55; 95% CI, 0.41–0.74; p &lt; 0.0001) Decreased infection rates for combination therapy vs oral monotherapy (RR = 0.34; 95% CI, 0.13–0.87; p = 0.02)</td>
</tr>
<tr>
<td>Englesbe</td>
<td>2010</td>
<td>1,553</td>
<td>SCIP-approved IV</td>
<td>Oral antibiotics + SCIP-approved IV</td>
<td>Yes</td>
<td>Decreased infection rates for combination therapy (4.6%) over monotherapy (8.6%) (p &lt; 0.001) Prolonged ileus less in combination therapy (3.8%) over monotherapy (8.9%) (p = 0.006)</td>
</tr>
<tr>
<td>Bellows</td>
<td>2011</td>
<td>2,669 in 16 trials</td>
<td>Meta-analysis</td>
<td>Meta-analysis</td>
<td>Undefined</td>
<td>Decreased infection rates for combination therapy over monotherapy (RR = 0.57; 95% CI, 0.43–0.76) NNT = 20 to prevent 1 surgical infection</td>
</tr>
</tbody>
</table>

NE, neomycin-erythromycin base; NNT, number needed to treat; RR, relative risk; SCIP, Surgical Care Improvement Practice.
Englesbe and colleagues\textsuperscript{22} showed no difference in \textit{C. difficile} infection when oral antibiotics were used compared with when they were not (1.3\% vs 1.8\%; \( p = 0.58 \)).

The relationship between oral antibiotics and mechanical bowel preparation with respect to postoperative complication rate is not entirely known. Nichols and colleagues\textsuperscript{14,39} showed that mechanical bowel preparation increased the serum and intracolonic concentrations of NE, however, these increased concentrations might not translate into significantly lower infection rates. Cannon and colleagues demonstrated that there was no difference in surgical site infection rates for patients receiving oral antibiotics alone vs those receiving oral antibiotics with mechanical bowel preparation (8.3\% vs 9.2\%; \( p = 0.47 \)).\textsuperscript{19}

Multiple theories for the decline of oral antibiotics exist. One is that physicians linked oral antibiotics with mechanical bowel preparation and did not think to use them independently. Another is that as pharmaceutical companies funded many studies of novel IV antibiotics, oral antibiotics simply were not getting the “publicity” of earlier studies. Also poor patient compliance might have led to the decline of oral antibiotic preparation; however, many studies have demonstrated a statistically significant decline in infections with prescribed oral antibiotics, regardless of compliance.\textsuperscript{2,19,20,22,46}

**CURRENT GUIDELINES**

Multiple societies and task forces have published guidelines and policies for perioperative antibiotic use in an attempt to standardize procedures and mitigate complications. In 1999, the CDC assembled the Hospital Infection Control Practices Advisory Committee to make recommendations in an attempt to reduce surgical site infections. They state that, in addition to IV antimicrobials and a mechanically cleansed colon, surgeons should “administer non-absorbable oral antimicrobial agents in divided doses on the day before the operation.” They classified the level of evidence as IA.\textsuperscript{32}

In 2003, the CDC and the Centers for Medicare and Medicaid Services created the Surgical Care Improvement Practice measures. According to the 2013 guidelines, IV antibiotics alone are recommended for colorectal procedures,\textsuperscript{47} despite the Discussion section that referenced data suggesting that oral antibiotic bowel preparation the day before surgery in addition to IV antibiotics has the lowest reported infection rate. Ironically, the colorectal section ends by stating, “In most patients, mechanical bowel preparation combined with a combination of oral neomycin sulfate plus oral erythromycin base or oral neomycin sulfate plus oral metronidazole should be given in addition to intravenous prophylaxis.”\textsuperscript{47} (Table 3). Philip Barie,\textsuperscript{57} editor of \textit{Surgical Infections}, expressed his agreement with this statement and even added, “who shouldn’t be protected thus?” with the use of oral antibiotics.

In a recent issue of \textit{Selected Readings in General Surgery}, a guide for surgeons on appropriate antibiotic usage recommended IV antibiotics alone before elective colon resection.\textsuperscript{56} The recommendation is derived from a study by Alexander and colleagues,\textsuperscript{58} which suggested IV cefazolin plus metronidazole or ertapenem alone as antibiotics for colon and rectal surgery. However, Alexander and colleagues’ recommendations were reproduced from findings of a Cochrane review conducted by Nelson and colleagues\textsuperscript{59} that states a “significant advantage to combined prophylaxis [oral plus IV] was found in the analysis (\( p < 0.0001 \)).” How Alexander and colleagues extrapolated recommendations from Nelson and colleagues’ data to subsequently result in what is published in \textit{Selected Readings in General Surgery} is unclear.

The Medical Letter recommends a combination of oral neomycin with either erythromycin or metronidazole and a parenteral agent of cefoxitin or cefotetan.\textsuperscript{55} The authors also advise against using ertapenem, suggesting it should be reserved for treatment of serious infections.\textsuperscript{8-31,50}

**CONCLUSIONS AND RECOMMENDATIONS**

Postoperative infections have a considerable impact on patient morbidity and mortality,\textsuperscript{1-3} especially in colorectal procedures, which have one of the highest incidences of infection.\textsuperscript{24} To provide the safest, most cost-effective care for patients, it is imperative to minimize the rate of postoperative infections. Although data and practice
recommendations remain inconclusive with respect to the use of mechanical bowel preparation, the conclusions from published data indicate the efficacy of preoperative oral antibiotics. Despite many oral medications having been studied, the literature suggests that NE are an effective choice for oral bowel preparation. Compared with other commonly used antibiotics, such as ciprofloxacin and metronidazole, neomycin is poorly absorbed by the gastrointestinal tract, and erythromycin, when absorbed, is found in high concentrations in the colon mucosa. Also, NE are inexpensive and readily available. Although erythromycin is known to have self-limiting side effects (eg, abdominal cramps, nausea, vomiting, and mild diarrhea) in approximately 10% of patients, it has a reputation as a safe nontoxic antimicrobial.

Based on this review of the literature and the history of preoperative bowel preparation for colorectal surgery, we recommend scheduled oral NE preparation, given in 1-g dosages at 1:00 PM, 2:00 PM, and 11:00 PM (6 g total), the day before surgery, in addition to perioperative IV antibiotics, as the best approach to minimizing surgical infections. In the United States, many hospitals follow Surgical Care Improvement Practice guidelines, which classify the lack of IV antibiotics as a “fallout.” Therefore, it would be impractical to propose a recommendation that did not include IV antibiotics. The combined oral and parenteral antimicrobial regimen has the theoretical advantage of providing intraluminal bacterial suppression as well as high serum and tissue antibiotic levels. The need for the use of oral antibiotics is clear throughout the presented literature. However, several questions remain. Do oral antibiotics need a mechanical preparation to be effective? Will the addition of IV antibiotics to oral antibiotics reduce the infection rate? We propose a 4-armed study. Two arms will have mechanical preparation and look at oral antibiotics with IV placebo vs oral and IV antibiotics. The second 2 arms will not have a mechanical preparation, but will look at oral antibiotics with IV placebo vs oral and IV antibiotics. Historically valid and recent studies have come out of the VA system, and we believe that the large network and the uniformity of the medical records make the VA an ideal place to conduct this prospective study.

**Author Contributions**

Study conception and design: Zelhart, Hauch, Slakey, Nichols

Acquisition of data: Zelhart, Hauch, Nichols

Analysis and interpretation of data: Zelhart, Hauch, Slakey, Nichols

Drafting of manuscript: Zelhart, Hauch, Nichols

Critical revision: Zelhart, Hauch, Slakey, Nichols

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**REFERENCES**


