PREOPERATIVE ANTIBIOTIC COLON PREPARATION: HAVE WE HAD THE ANSWER ALL ALONG?

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Abstract

Background: Colorectal surgery has some of the highest infection rates among elective operations. Decades of research have not resolved the controversy surrounding prophylactic antibiotic regimens, whether oral and/or intravenous, for colorectal surgery. Recent studies have shown that fewer surgeons are using scheduled oral antibiotics the day before surgery. Many published guidelines suggest the use of intravenous antibiotics only, despite the fact that data demonstrates lower infection rates when oral antibiotics are used, especially in combination with intravenous antibiotics. Some authors have begun to reexamine prophylactic oral antibiotic regimens and are renewing the debate on their efficacy at reducing infection-related complications following colorectal surgery. **Methods:** A critical review of the literature over the past six decades was undertaken. **Results:** Results from studies over the past six decades demonstrate statistically significant reductions or trends towards lower infection-related complications in colorectal surgeries among patient groups receiving preoperative prophylactic oral antibiotics or a combination of preoperative oral and intravenous antibiotics. **Conclusions:** Sufficient evidence exists that demonstrates combination therapy of scheduled preoperative oral and intravenous antibiotics results in the lowest rate of infection-related complications, despite the fact that scheduled oral antibiotics the day before colorectal surgeries has fallen out of favor with many surgeons. Furthermore, the combination of neomycin and erythromycin make an ideal prophylactic regimen because of their high concentrations in the colon, low cost, low resistance rate, and availability, in addition to the convincing evidence throughout the literature describing their ability at lowering infectious complications following colorectal surgery.

Key words: *Bowel preparation; Colorectal surgery; Oral antibiotics; Neomycin-erythromycin base*

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1. INTRODUCTION

The high rate of infection-related complications in colorectal surgery has a significant impact on morbidity, mortality, and cost [1]. Given the increasing emphasis on cost effectiveness and quality outcomes, minimizing infectious post-operative complications will influence physician credentialing and reimbursement in the future.

The evolution of bowel preparations prior to elective colorectal surgery spans at least sixty years. Decades of research on lowering the surgical infection rate have led to a variety of pre- and peri-operative 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, however, there is no consensus on best practice and therefore no standard to follow [2, 3].

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.

2. EVOLUTION OF APPROACHES TO PREOPERATIVE BOWEL PREPARATION

1950's - 1960's

In 1956, Cohn and colleagues found that

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oral neomycin and nystatin were effective in decreasing aerobic colonic bacteria in healthy humans [4]. In 1957, study of colon resections in dogs demonstrated that oral antibiotics improved survival and decreased anastomotic leaks [5, 6].

Early 1970's

Beginning in the early 1970's, Nichols and Condon demonstrated that oral antibiotics were likely indicated; however, the antibiotic regimens that were used at the time were not effective against the total colonic microflora [7].

Using a needle aspiration technique, in which fecal samples were obtained from the ileum, cecum, and transverse colon of patients undergoing elective cholecystectomy, they performed qualitative and quantitative analysis of the intestinal microflora. They demonstrated the colon possesses aerobic bacteria, but a predominance of anaerobic bacteria [8]. Commonly used oral antibiotic regimens at the time, such as neomycin, kanamycin, and the combination of neomycin and sulfathalidine, were ineffective in reducing the numbers of fecal anaerobes [9, 10].

Nichols and colleagues also researched mechanical bowel preparations and showed that although mechanical preparation was able to reduce fecal mass, it resulted in little reduction in the amount of aerobic and anaerobic flora within the colonic lumen [11]. They also demonstrated that the combination of neomycin and erythromycin base (NE) given in 1 gram dosages at 1:00 PM, 2:00 PM, and 11:00 PM (6 grams total) the day before surgery was able to significantly reduce fecal aerobic and anaerobic flora of the colon [12]. Other oral agents did not. Compared to mechanical preparation alone, preoperative administration of neomycin and erythromycin base in combination with mechanical bowel preparation resulted in significantly fewer wound infections. A prospective trial demonstrated a wound infection rate of 30% among ten patients receiving only mechanical cleansing compared to 0% for ten patients receiving combination therapy with the addition of oral antibiotics [13]. A total of 98 patients reviewed retrospectively were found to have wound infection rates of 17% with mechanical preparation only versus 0% when mechanical plus oral antibiotics were used [13].

Late 1970's - 1980's

In 1977, Nichols and co-workers found that mechanical bowel cleansing increased the concentration of intraluminal erythromycin base [14]. A series of large-scale, prospective, double-blinded, randomized Veterans Administration (VA) cooperative clinical trials were conducted. The first study by Clarke et al treated 116 patients with mechanical bowel preparation and either neomycin-erythromycin base (NE) or placebo [15]. Results demonstrated a significant difference in the rates of septic complications, such as intra-abdominal abscess, non-localized peritonitis, major anastomotic leak, fecal septicemia, or death due to sepsis, between the two groups with a 43% infectious complication rate in the placebo group compared to 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 [16].

The next two VA cooperative studies were published in 1978 and 1983 by Condon et al in an attempt to determine the effectiveness of parenteral antibiotic prophylaxis compared to the established oral neomycin-erythromycin base (NE) regimen (Table 1). These prospective double-blinded studies were performed in 16 VA hospitals and included 193 and 1128 patients, respectively [17, 18]. In the first study, intravenous 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 intravenous cephalothin. The parenteral arm was stopped after ten months because of data demonstrating ineffectiveness of intravenous 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, $p< 0.001$) [17]. The second study in 1983 demonstrated that the addition of parenteral antibiotics to oral NE had no significant effect on rates of wound infection or overall septic complications such as intra-abdominal abscess, non-localized peritonitis, major anastomotic leak, fecal septicemia, or death due to sepsis [18]. In this study, 1128 patients received mechanical cleansing and the NE preparation and were then randomized to receive

either intravenous 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) [18] (Table 1). However, in the patients having a rectal resection, the P value approached significance (p= 0.066) in favor of adding intravenous cephalothin [18].

In 1983, Kaiser et al conducted a prospective randomized study in which 119 patients received either IV cefoxitin only or the combination of neomycin-erythromycin base (NE) in addition to IV cefazolin. The authors showed that in surgeries lasting over 4 hours, patients with IV therapy alone had an infection rate of 37.5%, while those with combination therapy had an infection rate of 0% ($p < 0.05$) [19]. For all surgeries, 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 1980's, Lindsey and associates 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 [20]. Smith and co-investigators 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 over the previous two decades when using NE [21].

1990's

During the 1990's there were few significant studies investigating the use of antibiotics for colorectal surgery compared to the previous two decades [22]. 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 [23-28]. For example, Solla et al reported in 1990 that 92% of surgeons were using oral antibiotics [29] and Nichols et al published a survey of 471 surgeons demonstrating that 86.5% used oral with parenteral antibiotics [30].

A meta-analysis performed by Song and Glenny, showed that oral antibiotics alone were not as effective as when combined with parenteral [31]. In addition, Coppa and Eng documented increased rates of wound infection, intra-abdominal infection, and anastomotic leak when parenteral cefoxitin was used alone compared to combination with oral neomycin and erythromycin prophylaxis [32].

2000 - 2010

In 2000, Galandiuk noted that the advent of oral neomycin-erythromycin base (NE) was a significant contribution and one of the greatest advances to the safety of colon and rectal surgery [28]. NE are not antibiotics that are commonly used to treat infections thus making resistance less of a concern. Furthermore, NE have been used for decades without evidence of any major long-term side effects. At this time, Zmora conducted a survey of 515 colorectal surgeons in 2003, which showed that 75% used oral antibiotics routinely and an additional 11% used them selectively [33].

Several studies in this era evaluated the effectiveness and necessity of mechanical bowel preparation before elective colorectal surgery. In 2007, Jung et al 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 [34]. There were no significant differences between the two groups in infectious or cardiovascular complications. Several meta-analyses have reiterated this point [35-38].

Most papers 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 reduction of surgical site infection (SSI) [39-40]. Though these articles, by Itani and Wilson, are credited for bringing intravenous single-drug prophylaxis into its current popularity, neither of these studies allowed the use of oral antibiotics, preventing comparison to the prevailing standard combination therapy. It is curious that the jump to intravenous monotherapy commenced without clear data to support it. The infection rates in Itani's study were 26% for cefotetan and 17% for ertapenem [39], both higher than the infection rates repeatedly demonstrated for oral antibiotic regimens (<11%) [2, 19, 30, 41-46] (Table 2). Not surprisingly, given this shift in research the clinical use of oral antibiotics continued to decline. In 2010, Markell et al reported that only 36% of surgeons were using preoperative oral antibiotics, a significant decrease from the 1990's [47]. It appears that several factors led to this marked decline in oral antibiotic usage. First, Itani and Wilson's article received much attention throughout the medical community. In addition,

commercial pressures at that time pushed surgeons to use more intravenous antibiotics. Lastly, the need for mechanical preparation in colorectal surgery began to be questioned and many surgeons did not feel the need to include an oral antibiotic preparation if they were not going to give the patient a mechanical preparation, likely feeling that oral agents without mechanical preparation might not be effective [48].

Recently, there has been resurgence in studies touting the benefits of oral antibiotic preparation (Table 2). Starting in 2002, Lewis performed a randomized, double-blinded, placebo-controlled trial comparing combined antibiotics (oral neomycin and metronidazole with intravenous metronidazole and amikacin) versus intravenous antibiotics alone. Results demonstrated a significant decrease in infection rate in the combined group compared to intravenous antibiotics alone (4.5% vs. 16%, $p<0.01$) [41].

In 2009, Hayashi and Wilson commented that oral antibiotics form the crux for prophylaxis in elective colorectal surgery [48]. Interestingly, this statement comes following their study examining intravenous ertapenem versus cefotetan in 2006 in which oral antibiotics were completely excluded.

2010 and Beyond

Renewed interest in oral antibiotics is exemplified by Englesbe et al in their retrospective study of elective colectomies at 24 Michigan hospitals [42]. 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 et al performed a meta-analysis of 16 randomized controlled trials comparing combined oral and parenteral versus intravenous only antibiotics. They demonstrated a reduced risk of wound infections (RR: 0.57 [95% CI: 0.43–0.76], $p = 0.0002$; risk difference, −0.05 [CI: −0.08 to −0.02], $p = 0.0003$) compared with participants receiving only intravenous antibiotics. [43]. In 2011, a literature review by Fry also concluded that oral antibiotics needed to be added to surgeons' regimens for elective colorectal surgery [49].

In 2012, Cannon et al 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 to patients without oral bowel preparation and intravenous antibiotics alone (9.0% vs. 18.1%, $p< 0.0001$) [50]. Additionally, they showed total colectomy and rectal resections had higher risks of infection when compared to 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 [51]. Additionally, they showed that patients undergoing a total colectomy or rectal resection were at a higher risk for increased length of stay and readmission ($p<0.0001$) [51].

Deierhoi et al retrospectively examined 5,750 elective colorectal procedures [52]. This study showed that preoperative administration of combination oral and IV antibiotics resulted in a SSI 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 instance, the infection rate was 14.5% when ertapenem was given alone, but was 4.4% when oral antibiotics were given in combination [52]. Furthermore, Deierhoi found second-generation cephalosporins to be least effective, even though they are the principally recommended antibiotics in the Surgical Care Improvement Practice (SCIP) guidelines [44, 52]. This places doubt on the significance of Itani's 2006 study where intravenous ertapenem was deemed the antibiotic of choice despite the fact that oral antibiotics were not allowed in either arm of the study [39].

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 et al in 2005 [53], other recent and more powerful studies, such as the multicenter study of 2297 patients conducted by Krapohl et al in 2011, showed no statistical difference in the rates of *C. difficile* infection [54]. Another study by Englesbe and colleagues showed no difference in *C. difficile* infection when oral antibiotics were used compared to when they were not, 1.3% vs. 1.8% ($p = 0.58$) [42].

The relationship between oral antibiotics and mechanical bowel preparation with respect to postoperative complication rate is not entirely known. Nichols et al showed that mechanical bowel preparation increased the serum and intracolonic concentrations of NE; however, these increased concentrations may not translate into significantly lower infection rates [14, 34]. Cannon

et al demonstrated that there was no difference in surgical site infection rate for patients receiving oral antibiotics alone versus those receiving oral antibiotics with mechanical bowel preparation (8.3% vs. 9.2%, p= 0.47) [50].

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 intravenous antibiotics, so that oral antibiotics simply were not getting the "publicity" of prior studies. Also poor patient compliance may 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 [2, 42, 43, 50, 51].

3. CURRENT GUIDELINES

Multiple societies and taskforces have published guidelines and policies for perioperative antibiotic use in an attempt to standardize procedures and mitigate complications. In 1999, the Centers for Disease Control and Prevention (CDC) assembled the Hospital Infection Control Practices Advisory Committee (HICPAC) to make recommendations in an attempt to reduce surgical site infections. They state that in addition to intravenous 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 [27].

In 2003, the Centers for Disease Control and Prevention (CDC) and the Centers for Medicare and Medicaid Services (CMS) created the Surgical Care Improvement Practice (SCIP) measures. According to the 2013 guidelines, IV antibiotics alone are recommended for colorectal procedures [44], 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." [44] (Table 3). Philip Barie, editor of Surgical Infections, expressed his agreement with this statement and even added, "who shouldn't be protected thus?" with the use of oral antibiotics [55].

In a recent issue of Selected Readings in General Surgery (SRGS) a guide for surgeons on appropriate antibiotic usage [56] recommended IV antibiotics alone before elective colon resection. The recommendation is derived from a study by Alexander et al [57], which suggested intravenous cefazolin plus metridonazole or ertapenem alone as antibiotics for colon and rectal surgery. However, Alexander's recommendations were reproduced from findings of a Cochran review conducted by Nelson et al that states a "significant advantage to combined prophylaxis [oral plus IV] was found in the analysis ($p< 0.0001$)." [2]. How Alexander extrapolated his recommendations from Nelson's data to subsequently result in what is published in SRGS is unclear.

The Medical Letter recommends a combination of oral neomycin with either erythromycin or metronidazole and a parenteral agent of cefoxitin or cefotetan [58]. The authors also advise against using ertapenem, suggesting it should be reserved for treatment of serious infections. [23-26, 58].

4. CONCLUSIONS AND RECOMMENDATIONS

Post-operative infections have a significant impact on a patient's morbidity and mortality [1-3], especially in colorectal procedures, which have one of the highest incidences of infection[49]. To provide the safest, most cost effective care for patients, it is imperative to minimize the rate of postoperative infections.

While 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 to other commonly used antibiotics, such as ciprofloxicin and metronidazole, neomycin is poorly absorbed by the gastrointestinal tract and erythromycin, while absorbed, is found in high concentrations in the colon mucosa [14]. Also, NE are inexpensive and readily available. Although Erythromycin is known to have self-limiting side effects (abdominal cramps, nausea, vomiting, and mild diarrhea) in approximately 10% of patients, it has a reputation as a safe nontoxic antimicrobial [60].

Based upon this review of the literature and the history of preoperative bowel preparation for

colorectal surgery, we recommend scheduled oral NE preparation, given in 1 gram dosages at 1:00 PM, 2:00 PM, and 11:00 PM (6 grams total), the day before surgery, in addition to perioperative intravenous antibiotics, as the best approach to minimizing surgical infections [18, 42, 50, 51, 59]. In the United States many hospitals follow SCIP guidelines, which classify the lack of intravenous antibiotics as a "fallout." Hence, it would be impractical to propose a recommendation that did not include intravenous antibiotics. The combined oral and parenteral antimicrobial regimen has the theoretic 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 intravenous antibiotics to oral antibiotics further reduce the infection rate? We propose a four-armed study. Two arms will have mechanical preparation and look at oral antibiotics with intravenous placebo vs. oral and intravenous antibiotics. The second two arms will not have a mechanical preparation, but will look at oral antibiotics with intravenous placebo vs. oral and intravenous 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 record would make the VA an ideal place to conduct this prospective study.

REFERENCES

1. Dimick J, Chen S, Taheri P, Henderson W, Khuri S, Campbell D. Hospital costs are associated with surgical complications: a report from the private sector National Surgical Improvement Program. J Am Coll Surg. 2004; 199:531-537.
2. Nelson R, Glenny A, Song F. Antimicrobial prophylaxis for colorectal surgery. Cochran Database Syst Rev. 2009.
3. Hawn MT, Vick CC, Richman J, et al. Surgical site infection prevention: time to move beyond the surgical care improvement program. Ann Surg. 2011; 254:494-499.
4. Cohn I. Neomycin-nystatin for preoperative preparation of the colon. American Surgeon. 1956;22:301-7
5. Cohn I. Antibiotic support of colon anastamoses. Surg Gynecol Obstet. 1957; 104(1):1-7.
6. Cohn I. Intestinal Antisepsis. Springfield, IL Charles Thomas editor, p 1-245. 1968.
7. Nichols RL, Condon RE. Preoperative preparation of the colon. Surg Gynecol Obstet. 1971; 132:323-337.
8. Bentley DW, Nichols RL, Condon RE, Gorbach SL. The microflora of the human ileum and intra-abdominal colon: results of direct needle aspiration at surgery and evaluation of the technique. J Lab Clin Med. 1972; 79:421-429.
9. Nichols RL, Condon RE, Bentley DW, Gorbach SL. Ileal microflora in surgical patients. J Urol. 1971; 105:351-353.
10. Nichols RL, Condon RE. Antibiotic preparation of the colon: failure of commonly used regimens. Surg Clin North Am. 1971; 51:223-231.
11. Nichols RL, Gorbach SL, Condon RE. Alteration of intestinal microflora following preoperative mechanical preparation of the colon. Dis Colon Rectum. 1971; 14:123-127.
12. Nichols RL, Condon RE, Gorbach SL, Nyhus LM. Efficacy of preoperative antimicrobial preparation of the bowel. Ann Surg. 1972; 176:227-232.
13. Nichols RL, Broido P, Condon RE, Gorbach SL, Nyhus LM. Effect of preoperative neomycin-erythromycin intestinal preparation on the incidence of infectious complications following colon surgery. Ann Surg. 1973; 178:453-462.
14. Nichols RL, Condon RE, DiSanto AR. Preoperative bowel preparation: erythromycin base serum and fecal levels following oral administration. Arch Surg. 1977; 112:1493-1496.
15. Clarke JS, Condon RE, Bartlett JG, Gorbach SL, Nichols RL, Ochi S. Preoperative oral antibiotics reduce septic complications of colon operations: results of prospective, randomized, double-blind clinical study. Ann Surg. 1977; 186:251-259.
16. Bartlett JG, Condon RE, Gorbach SL, Clarke JS, Nichols RL, Ochi S. Veterans administration cooperative study on bowel preparation for elective colorectal operations: impact of oral antibiotic regimen on colonic flora, wound irrigation cultures and bacteriology of septic complications. Ann Surg. 1978; 188:249-254.
17. Condon RE, Bartlett JG, Nichols RL, Schulte WJ, Gorbach SL, Ochi S. Preoperative prophylactic cephalothin fails to control septic complications of colorectal operations: results of controlled clinical trial: a veterans administration cooperative study. Am J Surg. 1978; 137:68-74.
18. Condon RE, Bartlett JG, Greenlee H, et al. Efficacy of oral and systemic antibiotic prophylaxis in colorectal operations. Arch Surg. 1983; 118:496-502.
19. Kaiser AB, Herrington JL, Jacobs JK. Colorectal operations importance of the duration of the surgical procedure. Ann Surg. 1983; 198:525–529.

20. Lindsey JT, Smith JW, McClugage SG Jr, Nichols RL. Effects of commonly used bowel preparations on the large bowel mucosal-associated and luminal microflora in the rat model. Dis Colon Rectum. 1990; 33:554-560.
21. Smith MB, Goradia VK, Holmes JW, McCluggage SG, Smith JW, Nichols RL. Suppression of the human mucosal–related colonic microflora with prophylactic parenteral and/or oral antibiotics. World J Surg. 1990; 14:636-641.
22. Nichols RL. Bowel preparation. Scientific American Surgery. Chapter 4, Section VI (Perioperative Care). DW Wilmore, LY Cheung, AH Harken, JW, Holcroft, JL Meakins (Eds), Scientific American, Inc., New York, 1995.
23. Antimicrobial prophylaxis for surgery, Med Lett Drugs Ther. 1993. 35:91-4
24. Antimicrobial prophylaxis for surgery, Med Lett Drugs Ther. 1995. 37:79-82
25. Antimicrobial prophylaxis for surgery, Med Lett Drugs Ther.1997. 39:97-102
26. Antimicrobial prophylaxis for surgery, Med Lett Drugs Ther. 1999. 41:75-80
27. Mangram A, Horan T, Pearson M, Silver L, and Jarvis W. Guideline for prevention of surgical site infection, 1999. Inf Control Hosp Epidemiology. 1999. 20:247-78
28. Galanduik S and Mortensen N. Contributions of academic medicine to colon and rectal surgery. 2000. 43:1653-7.
29. Solla JA, Rothenberger DA. Preoperative bowel preparation. A survey of colon and rectal surgeons. Dis Colon Rectum. 1990; 33:154-159.
30. Nichols RL, Smith JW, Garcia RY, Waterman RS, Holmes JW. Current practices of preoperative bowel preparation among North American colorectal surgeons. Clin Infect Dis. 1997; 24:609-619.
31. Song F, Glenny AM. Antimicrobial prophylaxis in colorectal surgery: a systematic review of randomized controlled trials. Br J Surg. 1998; 85:1232-1241.
32. Coppa GF, Eng K. Factors involved in antibiotic selection in elective colon and rectal surgery. Surgery. 1988; 104:853-858.
33. Zmora O, Wexner S, Hajjar L, et al. Trends in preparation for colorectal surgery: survery of the members of the American Society of Colon and Rectal Surgery. Am Surg. 2003; 69:150-4.
34. Jung B, Pahlman L, Nystrom PO, Nilsson E, Mechanical Bowel Preparation Study Group. Multicentre randomized clinical trial of mechanical bowel preparation in elective colonic Resection. Br J Surg. 2007; 94:689-695.
35. Slim K, Vicaut E, Launay-Savary MV, Contant C, Chipponi J. Updated systematic review and meta-analysis of randomized clinical trials on the role of mechanical bowel preparation before colorectal surgery. Ann Surg. 2009; 249:203-209.
36. Gravante G, Caruso R, Andreani SM, Giordano P. Mechanical bowel preparation for colorectal surgery: a meta-analysis on abdominal and systemic complications on almost 5,000 patients. Int J Colorectal Dis. 2008; 23:1145-1150.
37. Pineda CE, Shelton AA, Hernandez-Boussard T, Morton JM, Welton ML. Mechanical bowel preparation in intestinal surgery: a meta-analysis and review of the literature. J Gastrointest Surg. 2008; 12:2037-2044.
38. Guenaga KK, Matos D, Wille-Jorgensen P. Mechanical bowel preparation for elective colorectal surgery. Cochrane Database Syst Rev. 2009.
39. Itani KM, Wilson SE, Awad SS, Jensen EH, Finn TS, Abramson MA. Ertapenem versus cefotetan prophylaxis in elective colorectal surgery. N Eng J Med. 2006; 355:2640-2651.
40. Wilson SE, Turpin RS, Kumar RN, et al. Comparative costs of ertapenem and cefotetan as prophylaxis for elective colorectal surgery. Surg Infect. 2008; 9:349-356.
41. Lewis RT. Oral versus systemic antibiotic prophylaxis in elective colon surgery : a randomized study and meta-analysis send a message from the 1990s. Can J Surg. 2002; 45:173–180.
42. Englesbe MJ, Brooks L, Kubus J, et al. A statewide assessment of surgical site infection following colectomy: the role of oral antibiotics. Ann Surg. 2010;252:514–519.
43. Bellows CF, Mills KT, Kelly TN, Gagliardi G. Combination of oral non-absorbable and intravenous antibiotics versus intravenous antibiotics alone in the prevention of surgical site infections after colorectal surgery: a meta-analysis of randomized controlled trials. Tech Coloproctol. 2011;15:385-395.
44. Bratzler DW, Dellinger EP, Olsen KM, et al. Clinical practice guidelines for antimicrobial prophylaxis in surgery. Surg Infect. 2013; 70:195–283.
45. Stellato T, Danziger L, Gordon N, et al. Antibiotics in elective colon surgery: a randomized trial of oral, systemic, and oral/systemic antibiotics for prophylaxis. Am Surg. 1990; 56:251-254.
46. Nichols RL, Choe EU, Weldon CB. Mechanical and antibacterial bowel preparation in colon and rectal surgery. Chemotherapy. 2005; 51:S115-S121.
47. Markell KW, Hunt BM, Charron PD, et al. Prophylaxis and management of wound infection after elective colorectal surgery: A survey of the American Society of Colon and Rectal Surgeons membership. J Gastrointest Surg. 2010; 14:1090-1098.
48. Hayashi MS, Wilson SE. Is there a current role for preoperative non-absorbable oral antimicrobial agents for prophylaxis of infection after colorectal surgery? Surg Infect. 2009; 10:285-288.
49. Fry DE. Colon preparation and surgical site

infection. Am J Surg. 2011;202:225–232.
50. Cannon JA, Altom LK, Deierhoi RJ, et al. Preoperative oral antibiotics reduce surgical site infection following elective colorectal resections. Dis Colon Rectum. 2012;55:1160–1166.
51. Toneva GD, Deierhoi RJ, Morris M, et al. Oral antibiotic bowel preparation reduces length of stay and readmissions after colorectal surgery. J Am Coll Surg. 2013;216:756–762; discussion 762–763.
52. Deierhoi R, Dawes L, Vick C, Itani K, and Hawn M. Choice of intravenous antibiotic prophylaxis for colorectal surgery does matter. J Am Coll Surg. 2013;217:763-9.
53. Wren S, Ahmed N, Jamal A, and Safadi B. Preoperative oral antibiotics in colorectal surgery increase the rate of Clostridium difficile colitis. Arch Surg. 2005;140:752-6.
54. Krapohl G, Phillips L, Campbell D, et al. Bowel preparation for colectomy and risk of Clostridium difficile infection. Dis Colon Rectum. 2011; 54:810-817.
55. Barie P. Guideline for antimicrobial prophylaxis in surgery: A must-read, must-heed for every surgeon. Surg Infect. 2013; 14(1):5-7.
56. Flint L. Surgical Infection. Selected Readings in General Surgery. 2013;39.
57. Alexander JW, Solomkin JS, Edwards MJ. Updated recommendations for control of surgical site infections. Ann Surg. 2011;253:1082–93.
58. Antibicrobial prophylaxis for surgery, Med Lett Drugs Ther. 2012. 10:73-78.
59. Fritze D, Englesbe MJ, Campbell DA Jr. Oral antibiotics to prevent surgical site infections following colon surgery. Adv Surg. 2011; 45:141–153.
60. Forrest G, Oldach D. Infectious Diseases, Chapter 22 Macrolides and Clindamycin. Lippincott Williams and Wilkins Gorbach S, Bartlett J, Blacklow N editors. p217.2004.

Table 1. Cooperative Trials among Veterans Administration (VA) Hospitals.

First Author	Year	n	First Study Arm	Second Study Arm	Mechanical Bowel Prep?	Findings
Clark[15]	1977	116	Mechanical prep with NE*	Mechanical prep with placebo	Yes	Sepsis rate of 43% in placebo group, 9% in NE group (p>0.0002)
Condon[17]	1978	193	IV cephalothin with oral placebo	Oral NE* with or without IV cephalothin/ placebo	Yes	Overall sepsis rates of 39% vs. 6% in oral NE* group (p< 0.001). Wound infection rates 30% vs. 6% in oral NE* group (p< 0.001).
Condon[18]	1983	1.128	Oral NE* + IV placebo	Oral NE* + IV cephalothin	Yes	Nonsignificant lower infection rates for combination (5.7%) over oral monotherapy (7.8%) (p= 0.22)
Itani[39]	2006	1.002	IV ertapenem	IV cefotetan	Yes	Surgical site infections 26.2% with cefotetan vs. 17.1% with ertapenem. ORAL ANTIBIOTICS NOT ALLOWED IN THIS STUDY
Cannon[50]	2012	9.940	SCIP** approved IV	Oral NE* or oral metronidazole/ neomycin + SCIP approved IV	73% received prep	Decreased infection rates for the combination therapy (9%) over monotherapy (18.1%) (p< 0.0001).
						In another endpoint, p= 0.47 for oral antibiotics vs. oral antibiotics with mechanical bowel prep.

First Author	Year	n	First Study Arm	Second Study Arm	Mechanical Bowel Prep?	Findings
Toneva[51]	2013	8.180	SCIP** approved IV	Oral NE* or oral metronidazole/ neomycin + SCIP approved IV	None 17.2% Mechanical alone 39% Oral antibiotics with or without mechanical prep 43.7%	Lowest infection rate for combination oral and IV therapy with mechanical prep. (8.6%) vs. IV monotherapy with mechanical prep. (19.5%) vs. IV monotherapy without mechanical prep. (18.6%) (p<0.0001)
Deierhoi[52]	2013	5.750	Combined Oral (NE* used in 74%) and SCIP** approved IV antibiotics	SCIP** approved IV antibiotics alone	undefined	Lower surgical site infection rate with combination antibiotics (6.3%) vs. IV antibiotics alone (16.7%) (p< 0.0001)

*NE= neomycin-erythromycin; **SCIP = Surgical Care Improvement Practice[42]

Table 2. Superiority of Oral and Parenteral Antibiotic Combination Therapy

First Author	Year	n	Monotherapy	Combined Therapy	Mechanical Bowel Prep?	Findings
Kaiser[19]	1983	119	IV cefoxitin	Oral NE* + IV cefazolin	Yes	Infection rate for combination therapy (3.2%) vs. monotherapy (12.5%) (p= 0.06). Procedures >4 hours had lower infection rates for combination therapy (0%) vs. monotherapy (37.5%) (p< 0.05)
Coppa[32]	1988	350	IV cefoxitin	Oral NE* + IV cefoxitin	Yes	Lower infection rates for all comers in combination group (5%) over monotherapy (11%). Procedures >215 min showed a much lower infection rate for combination (2%) over monotherapy (19%) (p < 0.05)
Stellato[45]	1990	169	IV cefoxitin alone or oral NE alone	Oral NE* + IV cefoxitin	Yes	Decreased infection rates for combination therapy (7.8%) compared to cefoxitin alone (11.7%) or NE alone (11.4%), not statistically significant

First Author	Year	n	Monotherapy	Combined Therapy	Mechanical Bowel Prep?	Findings
Lewis[41]	2002	208	IV amikacin/ metronidazole	Oral metronidazole/ neomycin + IV amikacin/ metronidazole	Yes	Surgical wound infections in (4.6%) of combination group and (16%) in monotherapy group (p< 0.01)
Nelson[2]	2009	182 trials, 30,880 pts	Meta-analysis	Meta-analysis	Undefined	Decreased infection rates for combination therapy compared to IV monotherapy (RR: 0.55, 95% CI: 0.41, 0.74, p< 0.0001). Decreased infection rates for combination therapy vs. oral monotherapy (RR: 0.34, 95% CI: 0.13, 0.87, p= 0.02)
Englesbe[42]	2010	1553	SCIP** approved IV	Oral antibiotics + SCIP** approved IV	Yes	Decreased infection rates for combination therapy (4.6%) over monotherapy (8.6%) (p< 0.001). Prolonged ileus less in combination therapy (3.8%) over monotherapy (8.9%) (p= 0.006)
Bellows[43]	2011	16 trials, 2.669 pts	Meta-analysis	Meta-analysis	Undefined	Decreased infection rates for combination therapy over monotherapy (RR: 0.57, 95%CI: 0.43, 0.76). NNT=20 to prevent 1 surgical infection

*NE= neomycin-erythromycin; **SCIP = Surgical Care Improvement Practice

Table 3. Current Guidelines on Antibiotics for Elective Colorectal Operations.

Organization	Recommendation
Surgical Care Improvement Practice (SCIP)[44]	Parenteral cefazolin + metronidazole, cefoxitin, cefotetan, ampicillin-sulbactam, ceftriaxone + metronidazole, ertapenem
The Medical Letter[58]	Oral neomycin + erythromycin/metronidazole and a parenteral agent of cefoxitin or cefotetan. Ertapenem not recommended.
American College of Surgeons Selected Readings[56]	Parenteral cefazolin + metronidazole or ertapenem alone
Hospital Infection Control Practices Advisory Committee (HICPAC)[27]	Parenteral antibiotics and non-absorbable oral antibiotics and mechanical bowel preparation