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REVIEW

# Role of oral antibiotics for prophylaxis against surgical site infections after elective colorectal surgery

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## Abstract

Over the past few decades, surgeons have made many attempts to reduce the incidence of surgical site infections (SSI) after elective colorectal surgery. Routine faecal diversion is no longer practiced in elective colonic surgery and mechanical bowel preparation is on the verge of being eliminated altogether. Intravenous antibiotics have become the standard of care as prophylaxis against SSI for elective colorectal operations. However, the role of oral antibiotics is still being debated. We review the available data evaluating the role of oral antibiotics as prophylaxis for SSI in colorectal surgery.

**Key words:** Colorectal; Anastomosis; Leak; Antibiotics; Bowel preparation



**Core tip:** The role of oral antibiotics to reduce surgical site infections (SSI) after elective colorectal surgery is not yet settled. The research in this area has been overshadowed by studies examining mechanical bowel preparation (MBP) and intravenous antibiotics. Existing data show that intravenous antibiotics are now considered standardized prophylaxis, and MBP is on the verge of being eliminated altogether. We review the available data evaluating the role of oral antibiotics as prophylaxis for SSI in colorectal surgery.

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## INTRODUCTION

Even in this modern era, surgical site infections (SSI) still occur in 26% of patients after elective colorectal resections[1]. When a SSI develops, it lengthens hospital stay, prolongs the recovery period and delays the commencement of adjuvant systemic therapy for malignancies[1]. In addition, the associated health care expenditure increases on average by $11000-40000.00 United States dollars[2]. Therefore, SSI prevention is an important area of medical research.

Despite the existence of evidence-based recommendations for prophylaxis[1-9], there is still a wide variation of clinical practices to prevent SSIs after elective colorectal surgery. Less than a decade ago, the combination of mechanical bowel preparation (MBP) and intravenous antibiotic was the commonest form of prophylaxis in the elective setting. However, the role of MBP is now questionable since several good quality studies have challenged its value[9-19]. If the present trend continues, it appears that patients undergoing elective colorectal surgery may not need any specific intervention to reduce infectious morbidity, except for a single dose of intravenous antibiotics at induction.

On the other hand, there are other interventions that might have been overlooked and it may be worthwhile to re-visit them in order to establish their value in the current era. In this review, we discuss the available methods of SSI prophylaxis in elective colorectal surgery comprehensively by analysing their historical evolution as well as their current value. The role of oral antibiotic prophylaxis is examined in this context.

## LITERATURE SEARCH

A systematic literature search was conducted using medical archiving platforms, including Pubmed, Medline, Google Scholar and the Cochrane database of Systematic Reviews. We searched for studies evaluating SSI prophylaxis in elective colorectal surgery using the following search terms: "surgical site, infection, prophylaxis, antibiotics, mechanical preparation, bowel, surgery, elective" and "oral antibiotics". The data is discussed below from a chronological perspective so that the reader will understand the evolution of SSI prophylaxis in elective colorectal surgery.

### *History of antibiotics in colorectal surgery*

In the pre-antibiotic era, elective colorectal surgery was plagued by infections and high overall morbidity. This contributed to mortality rates in excess of 40% in the 19th century. Since faeces was known to be heavily laden with bacteria, it appeared logical that reducing faecal load would reduce infectious complications. This was initially achieved using a diverting stoma proximal to the anastomosis and by leaving the surgical wound open for healing by secondary intention.

At the turn of the 20th century, surgeons also began to manipulate dietary intake and administer oral agents such as charcoal. Over the subsequent decades, MBP evolved and by the mid-20th century became standard practice in elective colorectal operations, although there was no clear evidence of its effectiveness.

During this era, antibiotics had not yet been developed. It was not until 1928 that Alexander Fleming discovered penicillin[20] - and its first recorded clinical use was on February 12, 1941 when it was administered to 43-year old Albert Alexander to treat a facial abscess in the United Kingdom[21]. The clinical application of this discovery ushered in the antibiotic era, when significant research into new antibiotics was launched.

In the next two decades, three classes of antibiotics were discovered that shaped the future of colorectal surgery: Aminoglycosides in 1943[22], macrolides in 1952[23,24] and polymixins in 1958[25]. These antibiotics all had poor enteral absorption and exerted their actions primarily in the bowel lumen.

Albert Schatz discovered streptomycin, the first aminoglycoside, which he isolated from Streptomyces griseus on October 19, 1943[25]. By binding to the 30S sub-unit of bacterial ribosomal RNA, streptomycin interferes with the coupling of tRNA, leading to inhibition of protein synthesis[25]. Its efficacy to treat tuberculosis was proven conclusively by the very first randomized, double-blinded, placebo-controlled trial on record, designed by Sir Geoffrey Marshall of the MRC Tuberculosis Research Unit[26]. It was also used to sterilize the colon as a part of MBP, but when Lockwood *et al*[27] evaluated its efficacy by culturing stool samples in 24 patients who were treated with oral streptomycin, they found that the reduction in intestinal flora was unreliable. There were insignificant reductions in 39% of clostridia, 50% of coliforms and 88% of streptococci[27]. More importantly, they demonstrated rapid development of resistant strains of *Escherichia coli* (*E. coli*) in the patients who showed a favourable early response[27]. Based on these results Lockwood *et al*[27] recommended reserving streptomycin for tuberculosis treatment rather than expend the drug to sterilize the bowel for surgery. When Selman Waksman isolated the second aminoglycoside, neomycin, from streptomyces fradiae in 1944[22], it naturally became the choice for bowel sterilization. It also found application in the treatment of hepatic encephalopathy by killing ammonia-producing bacteria in the gastrointestinal tract.

Colistin, the first polymixin to be discovered, was isolated from Bacillus polymyxa var. colistinus in 1949[25]. It acts by disrupting lipopolysaccharides in the bacterial cell membrane. It was popular to sterilize bowel because it was poorly absorbed enterally and quite effective against luminal gram-negative bacilli such as *E. coli, Klebsiella Spp* and *Pseudomonas Spp*.

McGuire *et al*[23] isolated Erythromycin, the first macrolide, from strains of streptomyces erythreus in 1952. Erythromycin, through an incompletely understood mechanism, also binds to bacterial rRNA and interferes with aminoacyl translocation, preventing coupling of tRNA and so inhibiting protein synthesis[24,28]. It was attractive

for colorectal surgery since it was poorly absorbed from the gut[28].

The discovery of these three new classes of antibiotics that were poorly absorbed from the gastrointestinal tract provided a new opportunity to reduce the colonic bacterial counts because they exerted their action primarily in the bowel lumen. But there were mixed results to control SSIs in this era because most of the drugs were only effective against gram-negative bacteria with little anti-anaerobic effect[29,30]. Therefore, the use of oral antibiotic prophylaxis was slow to gain traction. It was not until the 1970s that reproducible results were obtained showing benefit from oral antibiotic prophylaxis.

In 1973, Nichols *et al*[31] published their landmark paper in which the oral neomycin-erythromycin combination was administered in three doses over 19 h preoperatively. They randomized 20 patients undergoing elective colorectal surgery to MPB with and without the oral antibiotic regime. All patients had colonic samples taken intra-operatively for culture. Nichols *et al*[31] reported "luxuriant growth of aerobes and anaerobes" in the patients who had MBP alone with mean concentrations that were "similar to those normally found in stool". However, addition of the oral antibiotic regime significantly reduced colonic anaerobes, total aerobes, coliforms, streptococci, bacteroides and peptostreptococci[31]. It was not surprising, then, that the incidence of wound infections was significantly greater with MBP alone (30% *vs* 0%) - and cultures revealed that they were all due to *E. coli* and *Bacteroides fragilis*[31]. *Peptostreptococci* and *Clostridia* were also common pathogens in Nichols' subsequent study where they retrospectively evaluated erythromycin/neomycin regimes in 98 elective colectomies in a case-control study[31]. There was also a greater incidence of wound infections when MBP was used alone, without antibiotics, in this study (17% *vs* 0%)[31].

In 1978, Bartlett *et al*[3] carried out a prospective randomized trial across 10 Veterans Administration Hospitals to compare the oral neomycin/erythromycin regime *vs* placebo. The oral antibiotics significantly reduced the incidence of SSIs from 35% to 9% and anastomotic leaks from 10% to 0%[3]. Cultures of luminal contents showed that oral antibiotics significantly reduced the concentrations of both aerobes and anaerobes by approximately $10^5$ bacteria/mL at the time of operation and there was no notable emergence of resistant forms on post-operative samples[3].

There was now an accumulation of data to show that when oral antibiotics were administered after the colon was cleansed by MBP, there was a measurable decrease in SSIs associated with colorectal operations[3,32-35]. The findings were so impressive that in 1979, Proud and Chamberlain[36] wrote "there is no justification for including a placebo in trials of this nature. Nor is mechanical preparation of the bowel alone sufficient for patients about to undergo elective colonic surgery". By the late 1970s, there was wide acceptance of oral antibiotics for SSI prophylaxis. However, continued developments in intravenous antibiotics would soon dampen the enthusiasm for oral antibiotics.

clavulanate in 1981[37]. By the mid-1990s, intravenous antibiotics were rapidly being popularized. With convenient dosing regimes, reliable bioavailability profiles and a wider spectrum of coverage, these newer agents overshadowed the oral non-absorbable antibiotics.

Although Benjamin Duggar discovered aureomycin, the first tetracycline, in 1945[38], it was not available for clinical use until 1955[39] and only became popular as a broad-spectrum antibiotic in the 1970s[39]. Metronidazole had been used since 1959 for parasitic infestations but the anti-bacterial effect was not appreciated until 1962 when it was prescribed for trichomonal vaginitis and cured the patient of bacterial gingivitis[40]. Similarly, it was not until the 1970s that metronidazole became used as an anti-anaerobic drug[41] after Nastro *et al*[42] demonstrated an *in vitro* effect and Whelan *et al*[43] proved an anti-anaerobic effect in humans. By the late 1970s, intra-venous metronidazole and tetracycline regime were becoming popular for SSI prophylaxis.

Further change came with the development of the cephalosporins, a group of antibiotics that inhibited cell wall synthesis. Cephalothin, the original cephalosporin, became available in 1964[44] and was soon followed by second-generation cephalosporins that had a wider spectrum of gram-negative cover[45]. The cephalosporins became popular due to the powerful effects against gram-positive and gram-negative bacteria, especially with the extended spectrum of second and third generation drugs in the late 1970s. They were also attractive for patients with penicillin and tetracycline allergies because they had low cross-reactivity rates[46]. Campagna *et al*[46] reported that patients with penicillin allergies had 1% cross-reaction with first generation cephalosporins and "negligible" cross-reactivity with second-generation cephalosporins[46].

Aminopenicillin was the first β-lactam to be identified in 1961 but the clinically useful derivative, amoxicillin, only became available in 1972[37]. By inhibiting peptidoglycan cross-linking in bacterial cell walls, β-lactam antibiotics have activity against a moderate spectrum of gram-positive and gram-negative organisms. Amoxicillin fell out of favour when resistance emerged due to its susceptibility to β-lactamase produced by some organisms[37]. But in 1972 a potent β-lactamase inhibitor, clavulanic acid, was isolated from Streptococcus clavuligerus[37]. It was combined with amoxicillin to produce a combination that became available for clinical use in the United Kingdom as oral preparations in 1981 and intravenous preparations in 1985[37].

In the next few years, these new intravenous broad-spectrum agents were quickly adopted for prophylaxis against SSI at the expense of oral non-absorbable antibiotics[8].

### MBP

MBP was in routine use by the mid-20th century. A

variety of methods were employed including enemas, whole gut irrigation and/or cathartics. Several theories were proposed as the mechanisms through which MBP could reduce infectious morbidity: the empty colon was easier for the surgeon to handle, so improving technical creation of the anastomosis[47]; there would be no faecal bulk to mechanically shear the fresh anastomosis[48]; the absence of faeces would avoid intra-operative contamination that led to SSI[49]; the reduced colonic bacterial load would leave less organisms with opportunity to cause SSI[49,50]; and the resultant drop in luminal pH would reduce ammonia production that had a cytotoxic effect on colonic anastomoses[51,52].

Evidence supporting these concepts came primarily from small animal studies suggesting that MBP increased anastomotic bursting pressure (intra-luminal pressure needed to mechanically disrupt an anastomosis)[51-53] and reduced anastomotic leaks on imaging or *ex-vivo* inspection[53]. Perhaps the most convincing evidence to support MBP was published by O'Dwyer *et al*[53] in 1989. They randomized 36 dogs to low anterior resection with or without MBP. At post-operative day 9, dogs subjected to MBP had significantly less anastomotic leaks (13% *vs* 47%) and pelvic abscesses (6% *vs* 29%).

But in the latter part of the 20$^{th}$ century, anastomotic failure rates still ranged widely from 5%-30% despite routine MBP[54]. It also became increasingly apparent that there were undesirable effects from MBP, including fluid shifts, electrolyte disturbances, nausea, vomiting, abdominal pain and poor patient tolerability[55-57]. But it was the growing trauma experience with emergency surgery for penetrating colon injuries that prompted surgeons to seriously question MBP. Multiple reports surfaced revealing good outcomes after emergent surgery in unprepared colon with irregular lacerations, faecal contamination and significant delay before repair[58-60]. A Cochrane Systematic Review of all randomized controlled trials evaluating diversion *vs* primary repair for penetrating colon injuries settled this issue by showing that primary repair in unprepared bowel significantly reduced overall morbidity, infectious complications, dehiscence and wound complications[61].

These good outcomes prompted investigators to design prospective randomized blinded trials to evaluate MBP for elective colorectal surgery[55,62-69]. Three trials actually suggested that MBP was harmful[55,67,68]. Santos *et al*[67] randomized 149 patients to elective colorectal surgery with and without to MBP. They reported that MBP led to significantly more wound infections (24% *vs* 12%, $P < 0.05$) and a worrisome trend toward increased anastomotic leaks (10% *vs* 5%). Bucher *et al*[55], in their multicentre prospective randomized trial of 153 patients, also reported that the MBP group had significantly more wound abscesses (13% *vs* 4%; $P = 0.07$; RR = 1.58; 95%CI: 0.97-2.34), infectious morbidity (22% *vs* 8%; $P = 0.028$; RR = 1.58; 95%CI: 1.16-2.14), extra-abdominal complications (24% *vs* 11%; $P = 0.034$; RR = 1.5; 95%CI: 1.11-2.04) and prolonged hospital stay - even in the sub-group without complications (11.7 ± 5.2 d *vs* 9.1 ± 2.7 d; $P = 0.001$). Bucher *et al*[68] histologically examined macroscopically healthy colon at the proximal resection margins in 50 patients who had MBP in a blinded prospective randomized trial. They noted that MBP produced potentially deleterious microscopic changes, including greater loss of superficial mucus (96% *vs* 52%; $P < 0.001$), loss of epithelial cells (88% *vs* 40%; $P < 0.01$), significant mucosal inflammation (48% *vs* 12%; $P < 0.02$) and infiltration of polymorphonuclear cells (52% *vs* 8%; $P < 0.02$)[68].

Several large meta-analyses were then commissioned to evaluate the available data from the prospective trials that randomized patients to elective colorectal surgery with or without MBP[10-19,70]. The first few meta-analyses also suggested that MBP was harmful[10-13,70]. Three meta-analyses independently demonstrated a statistically significant increase in anastomotic leaks with MBP[11-13]. One meta-analysis demonstrated a significant increase in wound infections with MBP[70] and another demonstrated a significant increase in post-operative cardiac events[10]. More recent meta-analyses, however, that have included larger patient numbers and better trial designs have not corroborated the harmful effects, although they do provide robust level I evidence that there is no benefit to MBP prior to elective colorectal surgery[15-19].

Although it initially appeared logical that reducing faecal load in the colon would reduce infectious morbidity and anastomotic failures, current data does not support this logic. The prevailing theory to explain this is that a fundamental difference exists between in intra-luminal bacteria and mucosa-associated bacteria. Mucosa-associated bacteria are found within the epithelium and they may be adherent to or trapped in mucus lining the colonic wall. While MPB physically evacuates faeces and bacteria from the lumen, there is insignificant effect on mucosa-associated bacteria[71]. Smith *et al*[72] used animal models to study intra-operative colonic lavage. In their study, they used tissue cultures to quantitatively assess the counts of intraluminal and mucosa-associated bacteria. They demonstrated 10000-fold reductions in intraluminal bacteria but insignificant changes in mucosa-associated bacteria[72]. This strengthened the theory that the intra-mucosal environment was a separate ecologic niche[72].

The overwhelming data from well-designed good quality studies demanded that MBP be abandoned as a part of modern colorectal surgery. Currently MBP is relegated only to specific circumstances for patients with: Tumours < 2 cm diameter that may not be easily appreciated intra-operatively, intra-operative colonoscopy is required, a laparoscopic approach is used or restorative proctectomy is scheduled[55]. However, this paradigm change depleted the armamentarium in the quest to minimize infectious morbidity. In our search for other interventions to combat infection, it may be worth re-considering the use of non-absorbable antibiotics.

Firstly, surgeons reported encountering undigested capsules in the colon intra-operatively[73]. They argued that the timing, absorption and dose of oral antibiotics

were not sufficiently refined to allow for reliable tissue concentrations intra-operatively[73]. The mixed results from early trials gave credence to this argument and there was no available data to counter this argument.

Secondly, it became increasingly recognized that anaerobes were being cultured in 50%[74] to 90%[75] of SSIs after elective colonic operations[76-78]. However, effective anaerobic agents were not available until Nastro *et al*[43] demonstrated the anti-anaerobic effect of metronidazole *in vitro* in 1972, and in 1973 when Whelan *et al*[44] demonstrated the *in-vivo* effect against *Bacteroides fragilis* and *Clostridium welchii* from the colon. But this coincided with the advent of intravenous agents and the oral preparations were overshadowed as clinicians' focus shifted toward intravenous metronidazole coupled with the newer broad-spectrum agents.

The cephalosporins, β-lactams and clauvulanic acid were rapidly being developed in the 1970's and 1980's. They were more attractive than oral antibiotics because of their powerful action against a wide spectrum of gram-positive and gram-negative organisms, predictable drug kinetics and better bioavailability[73]. Oral antibiotics sustained a serious blow in 1998 when Song and Glenny[4] carried out a meta-analysis of all randomized controlled trials between 1984 and 1995 that evaluated antimicrobial prophylaxis against postoperative SSI after colorectal surgery. After evaluating many regimes, they declared that the following regimes were ineffective: Metronidazole alone, doxycycline alone, piperacillin alone, and oral neomycin-erythromycin combinations[4]. Song and Glenny[4] recommended prophylaxis with a single pre-operative dose of intravenous second generation cephalosporin coupled with metronidazole.

With the increasing complement of antibiotics, concerns over drug resistance deepened. Lockwood *et al*[27] had already demonstrated that *E. coli* rapidly developed resistance after brief exposure to oral streptomycin. In the 1970s Nichols *et al*[79], having popularized the erythromycin-neomycin regime[29-31], warned that it could suppress endogenous organisms leading to overgrowth of resistant organisms. In the 1980's reports of *Clostridium difficile*-related pseudomembranous colitis "due to intestinal antiseptics such as oral neomycin" began to surface[80,81]. Although several studies have since disproved the significance of the potential overgrowth of resistant organisms[31,82-84], the suggestion that oral antibiotics could be harmful certainly slowed the enthusiasm for its use.

The final blow came in the late 1990s with the surmounting challenges to MBP. Up to this point, oral antibiotics were administered after mechanical cleansing of the colon. So oral antibiotics fell further into disuse in the late 1990's when MBP was seriously challenged in emergency[38,39,61,85] and elective colorectal surgery[10-13,15-19,71]. Without prior MBP, the prevailing thought was that oral antibiotics could not clear organisms effectively if faeces remained in the lumen.

Because of these factors in the late 1990's, oral antibiotics were over shadowed and debate raged on about the optimal choice of Ⅳ antibiotics and MBP. Therefore, it was not surprising that the use of oral antibiotics in colorectal operations steadily declined over the past three decades from 86% in the 1990s[86] to 36% in 2010[87].

At the turn of the 21st century, a few prospective randomized trials attempted to evaluate the role of oral antibiotic prophylaxis[3,5,31,88-92]. However, there was great heterogeneity between the studies in antibiotic selection, methods of administration, dosing schedules and study protocols. Therefore, mixed results were obtained. Some prospective randomized trials showed no further reduction in SSI when oral antibiotics were added to MBP plus intravenous antibiotics[90,91]. However, when Lau *et al*[89] randomized 194 patients to MBP with either the standard oral erythromycin/neomycin combination, intravenous metronidazole/gentamicin or both oral plus intravenous antibiotics, they found a significantly greater incidence of SSI with MBP and oral antibiotics (27.4%) compared to intravenous antibiotics alone (11.9%) or combined intravenous-oral preparations (12.3%). This study provided conflicting results by now suggesting that oral antibiotics were harmful[89]. The findings also conflicted with the results of prospective randomized trials[3,5,31,88,92] that suggested significant reductions in SSI rates when oral plus intravenous antibiotics were used for prophylaxis. The presence of multiple randomized controlled trials with conflicting results prompted three groups to perform meta-analyses[1,5,8]. Table 1 evaluates the data from recent published meta-analyses evaluating oral antibiotic prophylaxis.

Lewis[5] published a meta-analysis in 2002 in which they examined randomized, controlled trials that compared 1077 patients receiving systemic antibiotics alone *vs* combined oral and intravenous antibiotics in 988 patients in order to prevent SSI in elective colorectal surgery between 1979 and 1995. They recorded SSIs in 6.88% of patients who received combined prophylaxis compared to 13.56% with intravenous antibiotics alone. The overall trend favoured combination therapy for prophylaxis, with a weighted mean risk difference for SSI of 0.56.

Bellows *et al*[1] published a meta-analysis in 2011 that included newer prospective randomized blinded trials[25] and only those that evaluated non-absorbable oral antibiotics. They evaluated 2669 patients across 16 randomized controlled trials comparing combined oral non-absorbable plus intravenous antibiotics *vs* intravenous antibiotics alone in elective colorectal surgery[1]. They found that the combination of oral non-absorbable plus intravenous antibiotics significantly reduced the risk of superficial and deep SSI compared to intravenous antibiotics only, although there was no effect on organ space infections or anastomotic leaks. Bellows *et al*[1] came to the same conclusion endorsing combined oral and intravenous antibiotics as prophylaxis during elective colorectal surgery.

Nelson *et al*[8] evaluated the effect of prophylactic

**Table 1 Published meta-analyses evaluating the use of oral antibiotics for surgical site infection prophylaxis in elective colorectal surgery**

| Ref. | Summary | Surgical Site Infections in patients who received antibiotic prophylaxis *via* | | | Strength/weakness of study | Conclusion |
|---|---|---|---|---|---|---|
| | | Combined oral + IV routes | IV route alone | Oral route alone | | |
| Lewis *et al*[5] (2002) | Meta-analysis of randomized trials comparing Ⅳ *vs* combined antibiotic prophylaxis in 2065 patients | 68/988 (6.88%) | 146/1077 (13.56%) | 0 | The major criticism was that they included studies that used absorbable and non-absorbable oral antibiotics. | Combination therapy significantly reduced overall SSI rates (RR = 0.51, 95%CI: 0.24-0.78; $P < 0.001$) *vs* Ⅳ antibiotics alone |
| Nelson *et al*[8] (2014 revision) | Metanalysis of 2929 patients across 15 randomized studies compared combined *vs* Ⅳ alone | 100/1456 (6.87%) | 188/1473 (12.76%) | 0 | All 13 trials were randomized controlled trials but only 5 were blinded studies<br>Some included MBP<br>Antibiotics not standardized<br>Included absorbable oral antibiotics | Combination therapy significantly reduced SSI rates (RR = 0.55, 95%CI: 0.43 to 0.71; $P = 0.0001$) compared to Ⅳ alone |
| Nelson *et al*[8] (2014 revision) | Metanalysis of 1880 patients across 9 randomized studies comparing combined oral + IV antibiotics *vs* oral alone | 39/943 (4.14%) | 0 | 74/931 (7.95%) | 7 studies used adequate randomization and 4 were blinded studies<br>Many study variables<br>Some included MBP<br>Antibiotics not standardized<br>Included absorbable oral antibiotics | Combination therapy significantly reduced SSI rates (RR = 0.52, 95%CI: 0.35 to 0.76; $P = 0.0003$) *vs* oral alone |
| Bellows *et al*[1] (2011) | Metanalysis of 2669 patients across 16 randomized trials comparing combined oral + Ⅳ antibiotics *vs* Ⅳ antibiotics alone | 91/1352 (6.73%) | 159/1317 (12.07%) | 0 | Only evaluated recent studies using non-absorbable oral antibiotics<br>7 were blinded studies<br>7 studies followed patients for hospital duration only | Combination therapy significantly reduced rates of superficial and deep SSI [RR = 0.57 (95%CI: 0.43–0.76), $P = 0.0002$; risk difference, -0.05 (95%CI: -0.08 to -0.02), $P = 0.0003$] *vs* IV alone<br>No difference in organ space infections [RR = 0.71 (95%CI: 0.43–1.16), $P = 0.2$] or anastomotic leaks [RR = 0.63 (95%CI: 0.28–1.41), $P = 0.3$] |

SSI: Surgical site infections; MBP: Mechanical bowel preparation.

antibiotics on SSIs in patients who underwent colorectal surgery in 24 randomized controlled trials. The latest 2014 revision of the Cochrane Systematic Review[8] proved that combined regimes of oral plus intravenous antibiotics provided better SSI prophylaxis than intravenous antibiotics alone or oral antibiotics alone. However, some of the individual studies that evaluated oral antibiotics were flawed, many including varied antibiotics and absorbable oral antibiotics and/or MBP. Nevertheless, Nelson *et al*[8] recommended the use of antibiotics covering aerobic and anaerobic bacteria to be delivered orally and intravenously prior to colorectal surgery for SSI prophylaxis.

Therefore, all 3 recently published meta-analyses[1,5,8] suggested that combined oral and intravenous antibiotics should be used for prophylaxis in elective colorectal surgery. Since these meta-analyses were published, further studies supporting the use of oral antibiotic prophylaxis[93-95] have been reported.

Toneva *et al*[93] retrospectively evaluated the post-operative course of 1161 patients who were readmitted to hospital after elective colorectal resections from 2005-2009. When they evaluated readmissions according to the type of prophylaxis used, it was noted that the patients who had oral antibiotic preparation had significantly less 30-day readmissions for infections (3.9% *vs* 5.4%; $P < 0.001$; OR = 0.81; 95%CI: 0.68-0.97) and a lower than average post-operative hospital stay than those who had MBP alone[93].

Canno *et al*[94] retrospectively studied 9,940 patients who underwent colorectal operations from 2005-2009 across 112 Veterans Affairs Hospitals where SCIP protocols were followed. They reported a significantly lower incidence of SSIs in the patients who had oral antibiotics alone (8.3%) compared to those who had MBP alone (18%) and those receiving no MBP (20%). This represented a 67% decrease in SSI (OR = 0.33; 95%CI: 0.21-0.50) when oral antibiotics were used. The use of oral antibiotics plus MBP resulted in 9.2% SSI rates, representing a 57% reduction in SSI occurrence (OR = 0.43; 95%CI: 0.34-0.55).

Sadahiro *et al*[95] evaluated 310 patients who underwent colonic resections for malignant disease who had MBP and intravenous flomoxef that were randomized to non-absorbable antibiotics antibiotics, probiotics or neither. They showed that oral non-absorbable antibiotic group had a significantly lower incidence of SSI (6.1% *vs* 18% *vs* 17.9% respectively). These patients also had a lower incidence of anastomotic leaks (1% *vs* 12% *vs* 7.4% respectively).

There is level Ⅰ evidence proving that intravenous

antibiotics are efficacious in reducing the incidence of SSI during elective colorectal surgery**.** Ideally, they should be administered intravenously, within 60 min of the surgical incision. A single pre-operative dose of a second or third generation cephalosporin (for extended gram negative coverage) combined with metronidazole (for anaerobic cover) is recommended for prophylaxis in elective colorectal surgery.

Good-quality data has now emerged supporting the role of oral antibiotics, in combination with intravenous antibiotics, for SSI prophylaxis. The existing data suggest that combination therapy is more effective than oral antibiotics alone and intravenous antibiotics alone. Therefore, in addition to the above intravenous regime, we also recommend administration of non-absorbable oral agents, such as neomycin sulphate with erythromycin, in the 18-h period prior to elective colorectal surgery.

We do recognize that the choice of antibiotics is still not yet settled, but it should include appropriate gram negative, gram positive and anaerobic coverage, with non-absorbable agents administered orally. The chosen regime should be guided by institutional antimicrobial protocols, taking into account the spectrum of microbes in the local environment, their resistance patterns and the availability of the individual agents.

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