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Review Article

Prevention of infectious complications after elective colorectal surgery in children: an American Pediatric Surgical Association Outcomes and Clinical Trials Committee comprehensive review

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ABSTRACT

Objective: This goal of this review was to examine the clinical evidence in support of commonly utilized measures intended to reduce complications following elective colorectal surgery.
Data source: Literature searches were performed to identify relevant studies from Medline, PubMed, and Cochrane databases.
Study selection: The American Pediatric Surgery Association Outcomes and Clinical Trials Committee selected eight questions to address this topic systematically in the context of three management areas: 1) appropriate utilization of systemic antibiotics for colorectal procedures, 2) reduction of stool burden through mechanical bowel preparation, and 3) intraluminal gut decontamination through use of enteral nonabsorbable antibiotics. Primary outcomes of interest included the occurrence of infectious and mechanical complications related to stool burden and intraluminal bacterial concentration (incisional surgical site infection, anastomotic leakage, and intraabdominal abscess).
Results: The evidence in support of each management category was systematically reviewed, graded, and summarized in the context of the review's primary outcomes. Practice recommendations were made as deemed appropriate by the committee.
Conclusions: Clinical evidence in support of interventions to reduce infectious complications following colorectal surgery is derived almost exclusively from the adult literature. High-quality evidence to guide clinical practice in children is sorely needed, as the available data may have only limited relevance to pediatric colorectal diseases.

Surgical site infections (SSIs) are a costly and potentially preventable source of morbidity, representing the most common cause of hospital-acquired infection in the surgical population [1–3]. Along the spectrum of elective procedures, colorectal operations have been associated with the highest risk of SSI and other infectious complications owing to the heavy bacterial load of the colon and rectum [3,4]. Although the rate of SSI associated with colorectal surgery is difficult to estimate, rates in excess of 25% have been reported from several large series [1,3]. Inpatient hospital costs for patients undergoing a colorectal procedure complicated by an incisional SSI are approximately twice that for patients without an SSI, and deep organ-space infections may increase costs by nearly four-fold [5–7]. Although these epidemiological data are derived exclusively from the adult population, bacterial colonization of the colon occurs by the second week of life, and the concentration and

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microbiological profiles of stool are similar in adults and children [8,9]. It is therefore likely that colorectal procedures are similarly responsible for a disproportionate burden of perioperative complications and excess hospital cost within the scope of pediatric surgical practice.

In response to the relatively high rate of morbidity associated with colorectal surgery, three main categories of prophylactic strategies have evolved with the goal of reducing infectious complications: 1) appropriate utilization of systemic antibiotic prophylaxis before, during, and following operative procedures, 2) reduction of stool burden through the use of mechanical bowel preparation, and 3) intraluminal decontamination of the colon and rectum through the use of enteral, nonabsorbable antibiotics. Although the pediatric surgical community has broadly adopted a consensus opinion favoring systemic antimicrobial prophylaxis for reducing infectious complications, there remains little agreement regarding the choice and optimal timing of these agents nor the role and efficacy of enteral antibiotics and mechanical bowel preparation as adjunct therapies [10,11]. Therefore, the purpose of this review was to examine the available evidence regarding these interventions (and combinations of interventions when available) and to propose recommendations based on the strength of available data. The American Pediatric Surgery Association Outcomes and Clinical Trials Committee selected the following eight questions to review the three categories cited above:

1. Which parenteral antibiotics should be used prophylactically and at what dose should they be administered?
2. When should parenteral antibiotics be administered relative to the operative incision for optimal prophylaxis?
3. How often should parenteral antibiotics be redosed during colorectal procedures?
4. How long should parenteral antibiotics be continued following colorectal procedures?
5. Does preoperative administration of enteral, nonabsorbable antibiotics combined with a mechanical bowel preparation reduce infectious complications?
6. Does the administration of preoperative mechanical bowel preparation without enteral antibiotics reduce infectious complications?
7. Does the administration of enteral antibiotics without a mechanical bowel preparation reduce infectious complications?
8. Does preoperative enema administration reduce infectious complications in colorectal procedures involving the rectum?

1. Methods

Literature searches were performed to identify English language publications using Medline, PubMed, and pertinent Cochrane reviews without a defined date range. Searches were conducted using the following search terms: colorectal surgery, antibiotic prophylaxis, infection control and prevention, mechanical bowel preparation, surgical site infection, anastomotic leakage, intraabdominal abscess and deep-space infection. Additional literature searches were conducted relating to the specific review questions. Studies were included in the review if they met criteria for providing either Class I or Class II evidence as defined by the Oxford Centre for Evidence-Based Medicine (Table 1) [12]. Very little data were found in the pediatric literature to support practice recommendations across all eight review questions, and none of the published studies including children provided Class I or higher-quality Class II evidence. However, given the similarities between the adult and pediatric populations with respect to fecal bacterial concentration and microbiological profiles, it was the committee's consensus that data from adult studies should be considered relevant to the pediatric population, and so chose to include adult-focused studies in this review. The primary outcomes of interest included infectious and mechanical complications plausibly related to stool burden and intraluminal bacterial concentration (incisional surgical site infection, anastomotic leakage and intraabdominal abscess). The evidence supporting each management question was reviewed and graded on the basis of established guidelines, and practice recommendations were made based on the strength of available evidence.

2. Literature review

2.1. Optimal use of parenteral antibiotics

The role of prophylactic intravenous antibiotic administration prior to elective colonic surgery is well established and has long been considered the standard of care in adult colorectal surgery. In a 2009 Cochrane review of ten clinical trials comparing outcomes in patients receiving parenteral antibiotic prophylaxis to none (or placebo), a significant reduction in the risk of SSI was observed in eight of the ten trials, with a reduction in relative-risk (RR) ranging from 59% to 88% [13–20]. A meta-analysis of all ten trials demonstrated a statistically significant benefit in favor of parenteral antibiotic prophylaxis, with a reduction in the aggregate SSI rate from 39% to 10% (RR 0.30, 95% CI 0.22–0.41) [21].

At the time of this review, no Class I data were available in the literature to make a similar statement regarding the efficacy of prophylactic antibiotics in pediatric colorectal surgery. No clinical trial was found that included children in the Cochrane review cited above or in a similarly directed MEDLINE search strategy when cross-referenced to the pediatric population. Pediatric surgeons have thus far had to rely on adult derived data to make choices regarding intravenous (IV) antimicrobial prophylaxis, and consequently, the data utilized to support the conclusions in the following section are derived almost exclusively from the adult literature.

2.1.1. Which parenteral antibiotics should be used prophylactically and at what dose should they be given?

Effective use of prophylactic IV antibiotics in elective colorectal surgery requires that the drug (or drugs) has activity against a broad range of colonic flora. Preoperative IV antibiotics used in elective colorectal surgery must therefore cover both the aerobic and anaerobic bacteria commonly found in the colon and rectum. Agents that solely target anaerobic or aerobic bacteria have been shown to be inferior to broad spectrum agents in a multitude of clinical trials and a large meta-analysis [21]. In a Cochrane review of 15 such trials, the addition of anaerobic coverage to antimicrobial agents primarily effective against aerobic organisms resulted in a nearly 50% further reduction in the risk of SSI for colorectal procedures (RR 0.55, 95% CI 0.35–0.85) [21]. Similarly, a nearly 60% further reduction in SSI rates was observed with the addition of aerobic gram-negative coverage to agents that principally covered anaerobic bacteria (RR 0.41, 95% CI 0.23–0.71) [21].

Although the efficacy of broad-spectrum IV antibiotic prophylaxis is now well-established, the optimal choice of antibiotic agents remains controversial. In a systematic review of 147 clinical trials including more than 70 antibiotic combinations, Song and Glenny found no significant differences in the prevention of SSIs within the majority of trials

Table 1
Grading classification for levels of clinical evidence and grades of recommendation according to the Oxford Centre for Evidence-based medicine*.

Classes of evidence	Grades of recommendation
I Systematic review of RCTs or with one RCT with narrow CI	A – Consistent Level 1 studies
II Cohort studies, low quality RCTs, outcomes research	B – Consistent Level 2 or 3 studies or extrapolation from Level 1 studies
III Case–control studies	C – Level 4 studies or extrapolations from Level 2 or 3 studies
IV Case series	D – Level 5 evidence or inconsistent or inconclusive studies
V Expert opinion	

RCT: randomized controlled trial, CI: confidence interval.
* www.cebm.net.

when the prophylactic regimens being compared carried activity against both anaerobic and aerobic organisms [22]. Although the studies included in the review were too heterogeneous in design and patient populations to support a formal meta-analysis, second generation cephalosporins (cefotetan and cefoxitin) given as single-agent prophylaxis appeared to be no less effective than newer generation cephalosporins, or to regimens which included metronidazole or gentamicin as "gold standard" agents against anaerobic and gram-negative organisms, respectively (Table 2). The simplicity of an economical single-drug regimen associated with a favorable side-effect profile resulted in cefotetan and cefoxitin becoming the most commonly used agents for the prevention of colorectal SSIs in the United States. Based on these studies and others, the Surgical Care Improvement Project (SCIP) evolved and provided a set of prophylactic antibiotic recommendations from their initial advisory statement. These recommendations became the basis for what are now known as the SCIP-2 guidelines for colorectal prophylaxis, currently endorsed by the Joint Commission (Table 3) [29].

Following dissemination of the initial SCIP guidelines in 2005, data began to emerge challenging the premise of equal efficacy among the SCIP-compliant antibiotics, and in particular, the "gold-standard" status of the second-generation cephalosporins. In 2006, Itani et al. reported the results of a randomized, double-blind trial comparing ertapenem to cefotetan prophylaxis in 1002 patients undergoing elective colorectal procedures [24]. A successful outcome was defined as the absence of SSI, anastomotic leakage, or antibiotic use four weeks postoperatively. After adjusting for patient and procedure-related factors, the failure rate was 28.0% in the ertapenem group and 42.8% in the cefotetan group (absolute difference: −14.8%; 95% CI: −21.9 to −7.5). In a study of 5750 patients undergoing colorectal procedures at 112 Veterans Affairs (VA) hospitals between 2005 and 2009, Deierhoi et al. found significantly higher SSI rates for all SCIP-compliant antibiotic regimens with the exception of ertapenem when compared to cefazolin with metronidazole as the SCIP reference regimen [30]. The results of this study were particularly compelling given that the data were not only adjusted for patient and hospital characteristics independently associated with SSIs, but also for the timing of antibiotic administration. In a retrospective analysis of prospectively collected data from the Michigan Surgical Quality Collaborative Colectomy Best-Practices Project, Hendren et al. compared the efficacy of different SCIP-compliant antibiotics in 4331 patients undergoing colorectal procedures between 2008 and 2010 [31]. After adjusting for patient factors, clustering, hospital-level effect, and compliance with other SCIP process measures, the authors found that only three of the eight SCIP-compliant antibiotic regimens (ciprofloxacin and metronidazole, cefazolin and metronidazole, and ertapenem) were associated with significantly lower SSI rates when compared to SCIP "noncompliant" regimens. Finally, in a large retrospective review of 5469 patients undergoing elective colorectal procedures from the VA Surgical Care Improvement Project Database (VASCIP), Hawn et al. explored the effect of antibiotic choice on SSIs after controlling for a multitude of patient, procedural and perioperative factors including the timing of antibiotic administration [32]. The authors found that the use of only two of the SCIP-compliant antibiotic regimens, cefazolin and metronidazole (OR 0.49, 95% CI 0.34–0.71) and fluoroquinolone and metronidazole (OR 0.55, 95% CI 0.35-0.87), was independently associated with a significant reduction in SSI risk. The collective results of these studies provide increasing evidence that not all SCIP-compliant antibiotics have equal efficacy. Furthermore, the commonly used second-generation cephalosporins may be inferior to their SCIP counterparts in preventing SSIs. This may also partially explain the lack of consistent data demonstrating that compliance with SCIP-approved antibiotic regimens results in lower SSI rates [33,34].

Although comparative data on the efficacy of SCIP-compliant antibiotics in the pediatric population are nonexistent, it is plausible that the differential efficacy observed in the adult literature may be generalizable to children in the absence of gross differences in local antibiotic resistance patterns. In this regard, although all of the SCIP-compliant antibiotics have been shown to be generally safe for use in the pediatric population, there is far less known (and perhaps greater controversy) about the use of ertapenem and fluoroquinolones as routine prophylactic agents in children. Given that these agents comprise two of the three regimens that have been shown to be most effective within the SCIP-compliant options, pediatric surgeons should be familiar with their safety profiles relative to children.

Although ertapenem is not recommended for patients under three months of age, several published trials have demonstrated its effectiveness and safety for treating serious bacterial infections in children [35,36]. However, concern remains regarding the routine use of ertapenem for prophylaxis owing to the public health implications of carbapenem-induced resistance as well as studies suggesting an increased risk for *Clostridium difficile* infection [24]. The use of fluoroquinolones in children has generally been cautioned secondary to the well-documented incidence of arthropathy in both animal models and clinical trials, although recent data suggest these concerns may be overstated. In a meta-analysis of 105 clinical trials using fluoroquinolones as primary treatment for bacterial infections in children, the incidence of arthropathy and related musculoskeletal complications was found to be only 1.6% [37]. Furthermore, the vast majority of events were mild in severity and symptoms resolved in all cases after discontinuation of the medication. These data would collectively suggest that the use of ciprofloxacin as single-dose prophylaxis in children should be safe and well-tolerated.

The surgeon may face a challenging dilemma when treating children with a documented beta-lactam allergy or when institutional resistance patterns preclude the use of a cephalosporin-based regimen (the third of the three options that have been shown to be most efficacious among the SCIP-endorsed options). Given the apparent superiority of ertapenem and fluoroquinolone-based regimens over the remaining SCIP-compliant alternatives, the use of these agents may be justified despite the risk of inducing microbial antibiotic resistance. Although we propose recommendations in this regard, we caution that these

Table 2
Randomized trials comparing second-generation cephalosporins to later generation cephalosporins and multiple-agent prophylactic regimens for elective colorectal procedures.

Standard	Comparison regimen	Trial/N	Trial favors (for SSI)	Reference
Cefoxitin	Cephalothin (1st generation cephalosporin)	Prospective randomized/77	Cefoxitin ($p < 0.02$)	Antonelli et al. [23]
Cefotetan	Ertapenem	Prospective, double blind, randomized/901	Ertapenem (26.2% cefotetan vs. 17.1% ertapenem); higher incidence of *C. difficile* infection in ertapenem	Itani et al. [24]
Cefotetan	Cefotetan + metronidazole	Prospective randomized/615	Neither	Morton et al. [25]
Cefoxitin	Ampicillin + metronidazole	Prospective block randomized/352	Neither	Rorbaek-Madsen et al. [26]
Cefmetazole	Flomoxef (4th generation cephalosporin)	Prospective, multicenter, double blind randomized/492	Neither	Shimizu et al.
Cefotetan	Alatrofloxacin	Prospective, multicenter, double blind randomized/492	Neither	Milson et al. [27]
Cefotetan	Piperacillin	Prospective randomized/153	Neither	Hershman et al. [28]

Table 3
Surgical Care Improvement Project (SCIP) recommendations for parenteral antibiotic prophylaxis prior to elective colon surgery (version 2010B).

No documented or suspected allergy to beta-lactam antibiotics:
Single agents: cefotetan, cefoxitin, ampicillin/sulbactam, ertapenem, OR Cefazolin + metronidazole*
Documented or suspected allergy to beta-lactam antibiotics: Clindamycin + ciprofloxacin, OR Clindamycin + gentamicin, OR Clindamycin + aztreonam, OR Metronidazole + gentamicin, OR Metronidazole + ciprofloxacin**

https://manual.jointcommission.org/releases/archive/TJC2010B1/ProphylacticAntibioticRegimenSelectionForSurgery.html.
* Recommended as first-line, single-dose systemic antimicrobial prophylaxis in children undergoing elective colorectal procedures.
** Recommended as first-line, single-dose prophylaxis in children with a documented or suspected allergy to penicillins and cephalosporins.

are only guidelines and that institutional practice should reflect local resistance patterns, infection control priorities, the specific population being treated, and thoughtful collaboration between surgeons and their hospital's infectious disease epidemiologist.

As with identifying the most effective prophylactic agents, we found no available clinical trial data in children to support recommendations regarding optimal dosing for colorectal procedures. We therefore recommend that dosing of the SCIP-compliant antibiotics follows current 2013 American Society of Health-System Pharmacists (ASHP) consensus recommendations for pediatric dosing [38] (Table 4).

2.1.2. When should parenteral antibiotics be administered relative to the operative incision for optimal prophylaxis?

The goal of antimicrobial prophylaxis is to achieve serum and tissue drug levels that exceed the minimum inhibitory concentration for organisms likely to be encountered during the operation both at the time of incision and for the duration of the operation. In general, the closer to the time of the incision that the antibiotic is given, the greater the likelihood of persistent tissue levels at the end of the operation and the lower infection risk. Over five decades ago, Burke demonstrated that experimental incisions contaminated with *Staphylococcus aureus* could not be distinguished from incisions that had not been contaminated when antimicrobial agents were administered before the incision [39]. In 1976, Stone et al. demonstrated the lowest SSI rates in patients undergoing gastrointestinal, biliary, and colon operations when antimicrobial agents were administered within one hour of the incision compared to 12 hours before incision, after the incision was made, and to patients receiving no prophylaxis [40]. Administration of the first antimicrobial dose after procedure completion resulted in SSI rates almost identical to patients who did not receive any prophylaxis [40].

Multiple studies have since supported the notion that antibiotic prophylaxis should be administered as close to the time of incision as possible. In a large multicenter study of 4472 patients undergoing nongastrointestinal surgery, an infection rate of 1.6% was found when the antibiotic was administered within 30 minutes of the incision compared with 2.4% when administered between 31 and 60 minutes prior to incision [41]. Although this difference was not statistically significant, a trend toward significance may suggest that the study was inadequately powered (OR 1.74, 95% CI 0.98–3.08). In a study of 6761 patients undergoing a wide range of general surgery procedures (including elective colorectal cases), Koch et al. examined the risk of SSIs in association with prophylaxis timing after adjusting for patient and procedure characteristics [42]. The authors identified a nonlinear relationship with increased reduction of SSI risk as administration neared the time of incision, with the greatest reduction predicted when antibiotics were given four minutes prior to incision. In a risk-adjusted, retrospective analysis of 605 patients undergoing elective colorectal procedures, Ho et al. found significantly greater odds of SSI when antibiotics were administered greater than 30 minutes before the incision (OR 1.733, 95% CI 1.017–2.954) [43].

Although the studies cited above provide compelling evidence that prophylactic antibiotics should be administered within 30 minutes of incision, other studies have challenged these findings. In a prospective cohort study of 3836 patients undergoing elective colorectal procedures, Weber et al. found a significant increase in the odds of SSI when antimicrobial prophylaxis was administered within 30 minutes (OR 1.95, 95% CI 1.4–2.8) of incision or between 60 and 120 minutes prior to incision (OR 1.74, 95% CI 1.0–2.9) when compared with the 30 to 59 minute pre-incision interval [44]. In the largest study to date examining prophylaxis timing with SSI risk, Hawn et al. examined 32,459 patients undergoing a wide range of elective surgical procedures from the VASCIP database and found no significant association between antibiotic timing and SSI risk during the 60-minute period prior to incision [32]. A lack of association was also found in a sub-group analysis of 5469 patients undergoing elective colorectal procedures [32].

The lack of consistency with reported outcomes in studies examining the relationship between SSI risk and prophylaxis timing likely reflects the complex relationship between antibiotic properties, operative procedure, and patient comorbidities, as well as other factors. As a general principle, it is intuitive that the prevention of SSIs should hinge around adequate tissue concentrations throughout the procedure while the wound is open and the risk of bacterial contamination persists. Until further data are available, we recommend administering antimicrobial prophylaxis within one hour of incision which reflects current guidelines endorsed by both SCIP and the ASHP [38].

2.1.3. When should parenteral antibiotics be redosed during elective colorectal procedures?

If the goal of intravenous antibiotic prophylaxis is to achieve serum and tissue drug levels that exceed the minimal inhibitory concentration for commonly encountered organisms during the entire operative procedure, the specific pharmacokinetic properties of the antibiotic agents being employed for this purpose should be considered. Repeat intraoperative dosing may be important in minimizing the risk of postoperative SSI for lengthy procedures. However, there are limited data addressing this issue. Given the lack of studies to guide clinical practice, current recommendations remain largely based on pharmacokinetic properties of the antibiotic agents in the context of patient characteristics that may alter normal physiologic clearance (e.g. renal failure).

The most comprehensive and updated recommendations in this regard can be found in the published 2013 ASHP therapeutic guidelines (Table 4). The redosing intervals are calculated based on the continuation of an operation beyond 2 half-lives of the specific antibiotic employed after the administration of the first dose (not time of incision), and assumes normal renal function. In cases where renal function is abnormal, and the half-life of the antimicrobial agent may be prolonged, consultation with the pharmacology service is recommended. Although creatinine clearance is not routinely calculated in children, pharmacokinetic data suggest that the calculation of creatinine clearance may be beneficial in establishing the appropriate dosing interval for children with impaired renal function [45,46].

2.1.4. How long should parenteral antibiotic prophylaxis be continued postoperatively for colorectal procedures?

The shortest effective duration of antimicrobial administration for preventing SSI has not been well characterized; however, evidence is increasing that postoperative antimicrobial prophylaxis is not necessary for most procedures and may be associated with an increased risk of acquired antimicrobial resistance and *C. difficile* colitis [21,47–49]. In a meta-analysis of 17 randomized trials comparing single preoperative dose of antibiotic prophylaxis with multiple dose regimens extending coverage into the postoperative period, pooled data failed to show any difference in the incidence of SSI between groups [50]. In 2009, a

Table 4
Recommended pediatric dosing parameters for parenteral antibiotics endorsed by the Surgical Care Improvement Project (SCIP) as appropriate prophylaxis for elective colorectal surgery.

Antibiotic	Recommended IV dose		Recommended redosing interval
	Adult	Pediatric*	
Cefoxitin	2 g	3 months or older: 30 mg/kg/dose Maximum 2 g per dose	2 hours
Cefotetan	2 g	30 mg/kg Maximum 2 g per dose	6 hours
Cefazolin	2 g; 3 g if patient weight ≥120 kg	30 mg/kg Maximum 1 g per dose (if >80 kg use 2 g)	4 hours
Metronidazole	500 mg	7.5 mg/kg Maximum 1 g per dose	N/A
Clindamycin	900 mg	20 mg/kg Maximum 600 mg per dose	6 hours
Gentamicin	5 mg/kg based on dosing weight (single dose)	2 mg/kg	N/A
Aztreonam	2 g	30 mg/kg Maximum 1 g per dose	2 hours
Ampicillin/sulbactam	3 g (ampicillin 2 g/sulbactam 1 g)	50 mg/kg of the ampicillin component	2 hours
Ertapenem	1 g	15 mg/kg**	N/A

Adopted from the 2013 American Society of Health-System Pharmacist published guidelines [38]. N/A = intraoperative redosing not required.
* Pediatric weight-based dosing should not be greater than adults.
** Not recommended for children under 3 months of age.

Cochrane review was published by Nelson et al. analyzing 25 clinical trials published between 1984 and 2000 [21]. Of these, three trials compared a single preoperative dose to preoperative plus any combination of intraoperative or postoperative regimens for colorectal procedures, and none demonstrated a decreased risk of SSIs with repeated dosing (RR 1.17, 95% CI 0.67–2.05).

Published in 2004, an advisory statement from the National Surgical Infection Prevention Project recommended prophylaxis to be less than 24 hours following surgery for most (noncardiothoracic) procedures [51]. This statement was based upon the available literature at the time, and continues to be endorsed by the ASHP, ISDA, SIS & SHEA and current SCIP guidelines [38]. Although these guidelines were derived from the adult literature, the committee believes they are relevant to the pediatric population and recommend they be followed until further data are available to suggest otherwise.

2.1.5. Section summary and recommendations

1. Parenteral antibiotic prophylaxis should include one of the SCIP-approved agents (Grade A recommendation based on Class I evidence for equivalence among the SCIP agents, Table 3). Although second-generation cephalosporins offer the convenience and cost benefit of single-agent prophylaxis, increasing data from the adult literature suggest they may be inferior to the multiagent SCIP regimens (Grade B recommendation based on an increasing body of Class II evidence). In patients with a suspected or documented beta-lactam allergy, ciprofloxacin combined with metronidazole should be considered as the next line of prophylaxis (Grade B recommendation based on an increasing body of Class II evidence to suggest superiority over other SCIP-compliant regimens). Pediatric dosing for all SCIP-compliant antibiotic agents should follow guidelines as currently endorsed by the ASHP (Table 4).
2. Until further data are available, administering prophylaxis within one hour of incision (2013 ASHP and SCIP guidelines) should be followed (Grade B recommendation based on Class II evidence). Administration of prophylaxis closer to incision (e.g. within 30 minutes) cannot be recommended at this time owing to conflicting evidence from multiple Class II studies.
3. In children with normal renal function, we recommend following the ASHP guidelines for redosing (Table 4). In cases where renal function is abnormal, and the half-life of the antimicrobial agent may be prolonged, consultation with the pharmacology service should be considered (Class V evidence).
4. Antibiotic prophylaxis should be discontinued within 24 hours of the end of surgery (Grade A recommendation based on Class 1 evidence).

2.2. Role and efficacy of mechanical bowel preparation and enteral antibiotics as prophylactic adjuncts to parenteral antibiotics

2.2.1. Does the administration of a preoperative mechanical bowel preparation without nonabsorbable enteral antibiotics reduce infectious complications?

The concept of mechanical bowel preparation (MBP) likely emerged from the earliest days of elective colorectal surgery when fecal contamination was associated with reported SSI rates as high as 90% [4]. Removing gross fecal material was a logical strategy to reduce the risk of bacterial contamination at the surgical site and therefore potentially reduce infections. Many surgeons believed that mechanical cleansing allowed for easier manipulation of the colon within the abdomen during laparotomy, but MBP has been utilized primarily for its theoretical benefits in the reduction of SSI risk. From the early 1930s on, MBP has become part of standard colorectal practice despite a paucity of randomized trials to validate its assumed benefits [4,52].

Multiple meta-analyses published over the past 10 years have analyzed the results of several prospective randomized trials addressing this question in adult patients. We will focus on the most recent meta-analysis from the Cochrane collaboration that was published in 2011 and incorporated the currently available trials [53]. In this review, the authors used prospective, randomized trials that compared any type of MBP to no mechanical prep. The methods used to cleanse the bowel included mannitol, polyethylene glycol, sodium phosphate solution, and some trials employed multiple agents. The primary outcome was anastomotic leakage. Secondary outcomes included mortality, peritonitis, reoperation, wound infection, infectious extraabdominal complications, and noninfectious extraabdominal complications. Data from 18 trials were included, which cumulatively enrolled 2906 patients with MBP compared to 2899 with no bowel preparation [54–75]. There was no significant difference in the primary outcome of anastomotic leakage. Overall anastomotic leakage was 4.4% with MBP and 4.5% without (OR 0.99, CI 0.74–1.31). Comparing anatomic subsets, anastomotic leakage for low anterior resection was 8.8% with MBP compared to 10.3% without (OR 0.88, CI 0.55–1.40). Leakage for colonic surgery was 3.0%

(47/1559) with MBP compared to 3.5% without (OR 0.85, CI 0.58–1.26). Analyzing the 9 trials with adequate randomization, there was no difference in either anastomotic leakage or wound infection [54,58–61,67,70,72,76]. There were also no significant differences between groups in the secondary outcomes, including mortality, peritonitis, reoperation or extraabdominal infections.

This meta-analysis demonstrated no benefit from MBP and replicated the findings of 3 other large meta-analyses (Table 5) [74,79,80]. Taken in aggregate, the authors concluded that MBP was not necessary before elective surgery involving the colon, and that no further trials were warranted. Notably, of the three trials in the meta-analysis that identified a significant difference in outcomes between groups, mechanical bowel preparation was actually associated with an increased risk of complications. It has been proposed that the increased risk of complications may be owing to two complementary mechanisms: 1) although MBP reduces overall stool burden, it does not decrease the bacterial concentration in the residual feces [81], and 2) use of MBP has been associated with increased risk of fecal spillage during elective colorectal procedures [82]. As there was clearly no benefit to MBP, the authors of the Cochrane review suggested that the surgeon may be able to reserve MBP for specific circumstances like small lesions that are difficult to palpate or an anticipated need for intraoperative colonoscopy [53].

Data for the use of MBPs in children are limited to a few retrospective studies. A retrospective series of 33 children who underwent elective intestinal operations of the colon and distal small bowel without MBP were compared to a group of 110 children who underwent MBP at a single institution [83]. Choice of MBP was at the surgeon's discretion, and no differences were found in the rates of SSI's or anastomotic leakage. In a recent retrospective study of children undergoing colostomy closure at three hospitals, 187 children receiving MBP were compared to 85 without an MBP [84]. Choice of MBP was at the surgeon's discretion, and the authors found that MBP use was associated with a greater risk for wound infection (14% vs. 6%, $p = 0.04$) and a longer hospital length of stay. In another retrospective study, 30 patients with no MBP were compared to 134 with MBP prior to colonic interposition for esophageal replacement in children [85]. The leak rate was 25% with MBP and 7% without ($p = 0.03$), further suggesting that, at best, MBP offers no clear benefit in reducing postoperative complications and may lead to worse outcomes.

2.3. Does the administration of enteral antibiotics without a mechanical bowel preparation reduce infectious complications?

There are currently very limited data to address this question in both the adult and pediatric colorectal literature. Evidence to suggest that enteral antibiotics may reduce the risk of SSIs without the need for a concomitant MBP would certainly be welcomed by both adults and children, although this would prove counterintuitive to the notion that reduction in stool burden is essential for enteral antibiotics to be effective. However, in the VASCIP study cited above by Canon et al., a subgroup of patients receiving only enteral antibiotics without MBP had a significantly lower risk of SSIs compared to the group of patients receiving no prophylaxis or MBP only [86]. When compared to the reference group of patients receiving neither MBP nor enteral antibiotics, the authors found that patients receiving enteral antibiotics only had a greater reduction in the odds of SSI compared with the group receiving both enteral antibiotics and MBP (OR 0.33; 95% CI 0.21–0.50 vs. OR 0.43, 95% CI 0.34–0.55). These groups (enteral antibiotics only versus enteral antibiotics combined with MBP) were not directly compared in the study to determine if they were statistically different, although these data would suggest that further investigation should explore what degree of mechanical bowel preparation is necessary for optimal prophylaxis using enteral antibiotics.

Table 5
Summary of published meta-analysis comparing rates of anastomotic leakage, surgical site infection and intraabdominal abscess between patients receiving preoperative mechanical bowel preparation (MBP) versus no preparation.

Outcome	No. included trials	MBP (n)/No MBP (n)	Peto OR [95% CI]
Anastomotic leakage			
Guenaga et al. [77]	13	2275/2258	0.99 [0.74, 1.31]
Cao et al. [78]	14	2682/2691	1.08 [0.82, 1.43]
Slim et al. [79]	14	2433/2381	1.12 [0.82, 1.53]
Pineda et al. [80]	13	2267/2263	1.21 [0.89, 1.64]
Wound infection or surgical site infection			
Guenaga et al. [77]	13	2305/2290	1.16 [0.95, 1.42]
Cao et al. [74]	14	2682/2691	1.26 [0.94, 1.68]
Slim et al. [79]	14	2452/2407	1.40 [1.05, 1.87]
Pineda et al. [80]	13	2304/2297	1.16 [0.95, 1.41]
Intraabdominal abscess			
Slim et al. [79]	10	2143/2088	0.90 [0.47, 1.72]

Peto OR = pooled odds ration from included trials. CI = confidence interval.

2.3.1. Does the administration of enteral antibiotics combined with mechanical bowel preparation reduce infectious complications?

Since the introduction of sulfanilamide into clinical practice over eight decades ago and the recognition that MBP did not reduce the concentration of colonic bacteria or SSI occurrence, surgeons have been exploring the utility of enteric administration of antibiotics for colonic decontamination [81,87]. The severity and frequency of infectious complications in colorectal procedures, the availability of novel and better tolerated antibiotics, and the observation from animal experiments that dramatic reductions in colonic bacterial density could be achieved with enteral antibiotics led to enthusiastic investigations of intestinal antisepsis using enterally administered agents in combination with mechanical bowel preparation [87,88]. Although Poth initially championed the concept of combining enteral antibiotics with mechanical preparation over five decades ago, Nichols popularized its clinical application after demonstrating a marked reduction in SSIs through several clinical studies in the 1970s [89–91].

Since Nichols' seminal publications, the clinical benefit of enteral antibiotics combined with MBP as an adjunct to intravenous antibiotics has been further confirmed through several randomized trials and meta-analyses. In what is currently the largest such meta-analysis, Bellows et al. analyzed 16 trials including a total of 2669 patients [92]. The authors found that the addition of enteral nonabsorbable antibiotics to standard parenteral antibiotic prophylaxis at the time of surgery reduced SSI risk by 43% compared with parenteral antibiotics alone (RR: 0.57; 95% CI 0.43–0.76, $p = 0.0002$). No differences were found in the risk of deep organ-space infections (RR 0.71; 95% CI 0.43–1.16, $p = 0.2$) or the risk of anastomotic leakage (RR 0.63; 95% CI 0.28–1.41, $p = 0.3$). The results of this meta-analysis were consistent with the findings of two other large meta-analyses that indicated a benefit with the use of enteral antibiotics (Table 6) [21,93]. Neomycin combined with erythromycin was the most common enteral oral antibiotic regimen used in the component studies in all three meta-analyses, although other combinations including metronidazole and kanamycin were also utilized.

More contemporary evidence to support the efficacy of combining enteral antibiotics with MBP has been shown in two large, multicenter prospective colorectal database studies [86,94]. As part of the Michigan Surgical Quality Colectomy Best Practices Collaborative Study, Englesbe et al. examined 2011 patients undergoing elective colorectal procedures at 24 hospitals between 2007 and 2009 [94]. Using propensity-matched analysis to adjust for factors that may have influenced the decision to use enteral antibiotics, as well as adjusting for patient, procedure, and process measure risk factors associated with SSI, the authors found a significant reduction in the rates of intraabdominal abscesses (1.8% vs. 4.2%, $p = 0.044$) and incisional SSIs (2.6% vs. 7.6%, $p = 0.001$) when enteral antibiotics were combined with MBP compared to MBP alone. Patients receiving enteral antibiotics also had similar rates of *C. difficile* colitis (1.3% vs. 1.8%, $p = 0.58$). In a study of 9940 patients from 112

VA hospitals between 2008 and 2009 included in the VA Colorectal SCIP database, Cannon et al. examined SSI rates between patients receiving MBP alone versus those receiving MBP and enteral antibiotics [86]. The majority of patients received a combination of neomycin and erythromycin (76%), while the remainder received a single agent. The most common enteral regimen given was neomycin combined with erythromycin (73% of patients) followed by neomycin combined with metronidazole (15%). After adjusting for patient, procedure, and perioperative risk factors known to be associated with SSI, the authors found that patients receiving enteral antibiotics combined with mechanical bowel preparation had a 57% decrease in the odds of surgical site infection compared with patients who received MBP alone (OR 0.43, 95% CI 0.34–0.55).

Relevant pediatric data are limited to small studies. In 1986, Debo Adeyemi et al. published a prospective study comparing the use of MBP alone versus MBP combined with various enteral antibiotics in 31 patients, of which 24 were children [95]. Although the study was small, the authors found a significantly lower infection rate in patients receiving an MBP combined with neomycin and metronidazole compared to those receiving MBP alone (40% vs. 6%, $p < 0.05$). In a retrospective review of 95 children undergoing colostomy closure following repair of imperforate anus, Breckler et al. compared 53 patients receiving an MBP combined with enteral antibiotics (neomycin or neomycin combined with erythromycin) to 42 patients receiving MBP only (based on surgeon preference) and found no difference in SSI rates between groups (MBP + enterals: 13% (7/53) vs. MBP alone: 17% (7/12)) [96]. In aggregate, the results from available pediatric studies do not provide a clear answer to this question. There remains a great need for prospective studies to explore whether the combined efficacy of oral antibiotics and MBP observed in the adult population can be extrapolated to children, and if so, how any benefit should be balanced against tolerance, quality of life, and safety considerations associated with this treatment for colorectal conditions in children.

2.3.2. Does preoperative enema administration reduce infectious complications in colorectal procedures involving the rectum?

The same Cochrane review of 18 trials cited in the previous section partially addressed this question by comparing MBP to enema administration in adult patients [53]. The subset of patients from 5 trials comparing 601 patients who underwent MBP with 609 patients allocated to 1 or 2 enemas was studied [55,57,63,65,66]. Overall, anastomotic leaks occurred in 4.4% of the MBP group and 3.4% of the enema group (OR 1.32, CI 0.74–2.36). For rectal procedures, specifically low anterior resection, 7.4% of 107 patients with MBP developed a leak compared to 7.9% of 88 patients with enemas (OR 0.93, CI 0.34–2.52) [55,57,65]. There were also no differences between groups with respect to mortality, peritonitis, reoperation, or wound infection, although these secondary variables were not analyzed specifically for rectal procedures. One trial within the review specifically investigated patients undergoing sphincter-sparing operations for rectal cancer and compared 89 patients who underwent MBP plus enema with 89 patients without any preparation; a higher rate of infectious complications was found in the group receiving no preparation [54]. There was also no difference in leakage rate, mortality, or hospital stay. A separate randomized trial from the Cochrane review compared 114 with MBP to 115 who received a single glycerin enema [85]. There were no differences in overall outcomes between groups, and within those undergoing low anterior resection, wound infections occurred in 7/33 with MBP and 8/40 with enema ($p = 1.0$).

The role for enemas compared to no preparation for rectal operations requires further investigation. If enemas and MBP are equivalent, and no preparation of any type is equivalent to MBP, then the utility of rectal enemas may be the same as no mechanical preparation of any type, but this has not been studied specifically. Currently, no published data specifically address the role of enemas for pull-through operations in children, and further studies are needed.

2.3.3. Section summary and recommendations

1. Use of MBP alone (without enteral antibiotics) for the indication of reducing infectious complications is not recommended as it provides no benefit over parenteral prophylaxis alone (Grade A recommendation based on Class I evidence from adult data). Data are limited in children but support the same recommendation (Grade C recommendation based on Class II/III evidence).
2. Available Class I evidence strongly supports the use of enteral antibiotics combined with an MBP for reducing SSIs in the adult population (compared with no preparation or MBP only), however, data are limited surrounding the efficacy and safety profiles of this practice for colorectal conditions in children. Further data are needed before a recommendation can be made (no recommendation).
3. Data are currently limited to support the use of enteral antibiotics alone (without concomitant MBP) in both adults and children. Further data are needed before a recommendation can be made (no recommendation).
4. Data are currently limited to support the routine use of enemas for colorectal procedures involving the rectum (no comparative effectiveness data exists for enemas vs. no enemas). Further data are needed before a recommendation can be made (no recommendation).

Table 6
Summary of published meta-analyses comparing rates of anastomotic leakage, surgical site infection and intraabdominal abscess between patients receiving enteral antibiotics combined with mechanical bowel preparation and versus those receiving parenteral antibiotics alone.

Outcome	No. included trials	Enteral + IV (n)/IV alone (n)	Peto OR [95% CI]
Anastomotic leakage			
Bellows et al. [92]	9	400/404	0.63 [0.28, 1.41]
Wound infection or surgical site infection			
Nelson et al. [21]	13	1176/1186	0.55 [0.41, 0.74]
Lewis et al. [93]	13	988/1077	0.56 [0.26, 0.86]
Bellows et al. [92]	16	1352/1317	0.57 [0.43, 0.76]
Intraabdominal abscess			
Bellows et al. [92]	10	951/926	0.71 [0.43, 1.16]

Peto OR = pooled odds ratio from included trials. CI = confidence interval.

3. Review summary and concluding remarks

The goal of this OCTC review was to provide a comprehensive summary of all available evidence that may be relevant to the prevention of infectious complications following colorectal procedures in children. The OCTC recognizes that the current body of clinical evidence cited in this review is derived almost exclusively from the adult population, and high-quality clinical outcome data to guide clinical practice in children are sorely needed. Until further data are available, we caution the reader that the recommendations offered in this review should only be used as guidelines. Decisions surrounding the use of parenteral antibiotics, mechanical bowel preparation and nonabsorbable antibiotics should carefully consider the potential relevance of these guidelines to specific clinical situations.

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