Current Common Dilemmas in Colorectal Surgery

Christopher M. Schlachta
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Editors
Christopher M. Schlachta
University Hospital
London Health Sciences Centre
London, ON, Canada

Patricia Sylla
Mount Sinai School of Medicine
New York, NY, USA

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For Paul, Jonah, Ariel, Mark, William, and Mary Lynn.

Preface

In April 2015, the Society of American Gastrointestinal and Endoscopic Surgeons (SAGES) sponsored a symposium at the annual meeting, held in Nashville, Tennessee, entitled "Current Common Dilemmas in Colorectal Surgery." The symposium was divided into three sessions that tackled common controversies related to selecting the most appropriate surgical treatment for various colorectal pathologies, the role of novel technologies and techniques to assist in their surgical management, and intraoperative strategies to overcome complications during routine and complex colorectal surgery. The success of the symposium inspired this textbook, which has the objective of providing a comprehensive and up-to-date overview by experts of current recommendations and strategies in the management of common colorectal pathologies.

Following the introduction of laparoscopic colon surgery, it has often been heard that the surgical community is waiting for the "next big thing." The reality is that, like all scientific advancements, major change occurs through a series of small steps. The evolution of care for patients with colorectal disease continues to evolve dramatically on several fronts prompting us to deliver this text in nine sections.

From optimizing preoperative bowel preparation to adoption of enhanced recovery pathways, the various strategies to minimize the perioperative morbidity of colorectal surgical procedures are extensively reviewed, with emphasis on the current standards and controversies in the endoscopic management of colorectal neoplasia. With respect to colorectal emergencies such as perforated diverticulitis and *Clostridium difficile* colitis, the role of minimally invasive and organ-preserving strategies is reviewed including various intraoperative strategies to optimize outcomes.

With respect to common pelvic floor disorders encountered in colorectal practice such as obstructed defecation, rectal prolapse, and fecal incontinence, the diagnostic workup and therapeutic options are reviewed, as are dilemmas regarding the role of surgery and optimal surgical approach when appropriate. With respect to other common colorectal pathologies such as symptomatic parastomal hernia, the role of hernia prevention and optimal strategies for repair is covered, as are recent trends in minimally invasive techniques applied to colorectal surgery, including the techniques and impact of intracorporeal anastomosis and natural orifice specimen extraction.

Finally, current controversies regarding the management of rectal cancer, including dilemmas related to selection and impact of neoadjuvant therapies, are extensively reviewed. The various strategies for sphincter preservation and abdominoperineal resection (APR), as well as various techniques to perform total mesorectal excision (TME), are reviewed at length, including the evolving role of transanal TME (taTME).

London, ON, Canada — Christopher M. Schlachta
New York, NY, USA — Patricia Sylla

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We would like to share our mutual admiration and respect that developed while co-chairing the SAGES 2015 Current Common Dilemmas in Colorectal Surgery Symposium and which has grown into an incredible partnership in this project. We would also like to thank Michael Griffin from Springer who has guided us in harnessing the success of the symposium and helping infuse it back into this textbook. We would also like to thank SAGES for supporting high-quality educational symposia and initiatives and for its unwavering commitment to support general and colorectal surgeons in bridging the gap in adopting minimally invasive surgery. Finally, we would like to acknowledge our families who generously allow us to take time away from them to be applied to these passionate academic pursuits.

Contents

Part II Endoscopic Approaches for Colorectal Neoplasia

Contributors

Nawar A. Alkhamesi Department of Surgery, University Hospital, London Health Sciences Centre, London, ON, Canada

Nicholas Gerard Berger Department of Surgery, Division of Colorectal Surgery, Medical College of Wisconsin, Froedtert Memorial Lutheran Hospital, Milwaukee, WI, USA

Joshua I.S. Bleier Department of Surgery, PENN Presbyterian Medical Center, Philadelphia, PA, USA

Luigi Boni Department of General and Emergency IRCCS-Ca' Granda-Policlinico Hospital, University of Milan, Milan, Italy

Marylise Boutros Division of Colon & Rectal Surgery, Jewish General Hospital, McGill University, Montreal, QC, Canada

Liliana Bordeianou Department of General Surgery, Massachusetts General Hospital, Boston, MA, USA

Carl J. Brown Department of Surgery, St. Paul's Hospital, University of British Columbia, Vancouver, BC, Canada

Maria Emilia Carvalho e Carvalho Division of Colorectal Surgery, Mater Dei Hospital, Belo Horizonte, MG, Brazil

Daniel T. Chang Department of Radiation Oncology, Stanford Cancer Institute, Stanford, CA, USA

Quentin Denost Department of Colorectal Surgery, Magellan Centre, Bordeaux University Hospital, Pessac, France

Tony Dixon Department of Colorectal Surgery, North Bristol NHS Trust, Southmead Hospital Bristol, Bristol, UK

Liane S. Feldman Department of Surgery, McGill University Health Centre, Montréal, QC, Canada

Abe Fingerhut Department of Surgery, University Hospital of Graz, Graz, Austria

James Fleshman Department of Surgery, Baylor University Medical Center, Dallas, TX, USA

Morris E. Franklin Jr. Minimally Invasive Surgery, Texas Endosurgery Institute, San Antonio, TX, USA

Krishna C. Gurram Department of Gastroenterology, Winthrop University Hospital, Mineola, NY, USA

Brooke H. Gurland Department of General Surgery, Division of Colorectal Surgery Stanford University, Palo Alto, CA, USA

Kristina L. Guyton Department of Surgery, The University of Chicago Hospitals, Chicago, IL, USA

Viktor Justin Department of Surgery, Section for Surgical Research, Medical University of Graz, Graz, Austria

Angelita Habr-Gama Department of Surgery, Angelita and Joaquim Gama Institute, São Paulo, Brazil

Birgitta M.E. Hansson Department of Surgery, Canisius-Wilhelmina Hospital Nijmegen, Nijmegen, The Netherlands

Miguel A. Hernández Minimally Invasive Surgery, Texas Endosurgery Institute, San Antonio, TX, USA

Torbjörn Holm Section of Coloproctology, Department of Surgical Gastroenterology, Karolinska University Hospital, Stockholm, Sweden

Roel Hompes Department of GI and Oncologic Surgery, Academic Medical Center Amsterdam, Amsterdam, The Netherlands

Neil H. Hyman Department of Surgery, The University of Chicago Hospitals, Chicago, IL, USA

Steven H. Itzkowitz Division of Gastroenterology, Icahn School of Medicine at Mount Sinai Hospital, New York, NY, USA

John T. Jenkins Department of Surgery, St. Marks Hospital, London, UK

Maria Abou Khalil Division of General Surgery, McGill University, Montréal, QC, Canada

Albert C. Koong Department of Radiation Oncology, MD Anderson Cancer Center, Houston, TX, USA

Lawrence Lee Department of Surgery, McGill University Health Centre, Montréal, QC, Canada

François Letarte Department of Surgery, St. Paul's Hospital, University of British Columbia, Vancouver, BC, Canada

Paula Loughlin Department of Surgery, Altnagelvin Hospital, Derry, UK

Kirk A. Ludwig Department of Surgery, Division of Colorectal Surgery, Medical College of Wisconsin, Froedtert Memorial Lutheran Hospital, Milwaukee, WI, USA

James F. Marion Division of Gastroenterology, Icahn School of Medicine at Mount Sinai, New York, NY, USA

John H. Marks Marks Colorectal Surgical Associates, Lankenau Institute for Medical Research, Wynnewood, PA, USA

Division of Colorectal Surgery, Lankenau Medical Center, Wynnewood, PA, USA

Elisabeth C. McLemore General Surgery, Kaiser Permanente, Los Angeles Medical Center, Los Angeles, CA, USA

John Migaly Department of Surgery, Duke University Medical Center, Durham, NC, USA

Peter Alexander Newman Department of Colorectal Surgery, North Bristol NHS Trust, Southmead Hospital Bristol, Bristol, UK

O.N.M. Panton Division of General Surgery, Vancouver General Hospital, Vancouver, BC, Canada

Ian M. Paquette Division of Colon and Rectal Surgery, University of Cincinnati Medical Center, Cincinnati, OH, USA

Srikanth Parsi Marks Colorectal Surgical Associates, Lankenau Institute for Medical Research, Wynnewood, PA, USA

Division of Colorectal Surgery, Lankenau Medical Center, Wynnewood, PA, USA

Marta Penna Department of Colorectal Surgery, Oxford University Hospital, Oxford, UK

Rodrigo Oliva Perez Department of Surgery, Angelita and Joaquim Gama Institute, São Paulo, Brazil

Andrea M. Petrucci Department of Colorectal Surgery, Cleveland Clinic Florida, Weston, FL, USA

Nicolas D. Prionas Department of Radiation Oncology, Stanford Cancer Institute, Stanford, CA, USA

Teresa C. Rice Department of Surgery, University of Cincinnati Medical Center, Cincinnati, OH, USA

Timothy J. Ridolfi Department of Surgery, Division of Colorectal Surgery, Medical College of Wisconsin, Froedtert Memorial Lutheran Hospital, Milwaukee, WI, USA

Cecilia Beatriz Rossi Department of Surgery, Angelita and Joaquim Gama Institute, São Paulo, Brazil

Eric Rullier Department of Colorectal Surgery, Magellan Centre, Bordeaux University Hospital, Pessac, France

Patrick Vincent Saitta Department of Internal Medicine, Division of Gastroenterology, Winthrop University Hospital, Mineola, NY, USA

Jean Salem Marks Colorectal Surgical Associates, Lankenau Institute for Medical Research, Wynnewood, PA, USA

Division of Colorectal Surgery, Lankenau Medical Center, Wynnewood, PA, USA

Barry Salky Department of Surgery, Mount Sinai Health System, New York, NY, USA

Julia Saraidaridis Division of Colon and Rectal Surgery, Lahey Clinic, Burlington, MA, USA

Guilherme Pagin São Julião Department of Surgery, Angelita and Joaquim Gama Institute, São Paulo, Brazil

Shailja C. Shah Division of Gastroenterology, Icahn School of Medicine at Mount Sinai Hospital, New York, NY, USA

Nishit Shah Rhode Island Hospital, Providence, RI, USA

Skandan Shanmugan Department of Surgery, PENN Presbyterian Medical Center, Philadelphia, PA, USA

Stavros N. Stavropoulos Division of Digestive and Liver Diseases, Columbia University Medical Center, New York, NY, USA

Division of Gastroenterology, Hepatology, & Nutrition, NYU Winthrop Hospital, Mineola, NY, USA

Adam T. Stearns Department of Surgery, Norfolk and Norwich University Hospitals NHS Foundation Trust, Norwich, Norfolk, UK

Zhifei Sun Department of Surgery, Duke University Medical Center, Durham, NC, USA

Joana Torres Division of Gastroenterology, Icahn School of Medicine at Mount Sinai Hospital, New York, NY, USA

Megan Turner Department of Surgery, Duke University Medical Center, Durham, NC, USA

Ryan C. Ungaro Department of Gastroenterology, Icahn School of Medicine at Mount Sinai, New York, NY, USA

Selman Uranues Department of Surgery, University Hospital of Graz, Graz, Austria

Bruna Borba Vailati Department of Surgery, Angelita and Joaquim Gama Institute, São Paulo, Brazil

Katerina Wells Department of Surgery, Baylor University Medical Center, Dallas, TX, USA

Steven D. Wexner Department of Colorectal Surgery, Cleveland Clinic Florida, Weston, FL, USA

Albert M. Wolthuis Abdominal Surgery, University Hospital Leuven, Leuven, Belgium

Susana Wu General Surgery, Kaiser Permanente, Los Angeles Medical Center, Los Angeles, CA, USA

Part I

Perioperative Preparation and Care

To Prep or Not to Prep

1

Nishit Shah

Introduction

Oral mechanical bowel preparation (OMBP) has been employed for elective colorectal surgery for many years. The rationale for its use, based on early observational data as well as long-standing expert and intuitive opinion, was that by removing the fecal load from the colon lumen prior to surgery, infectious complications and overall morbidity would be lowered. This led to the widespread adoption of OMBP, a clinical practice which is still in place for the majority of colorectal surgeries in the United States today [1].

Since approximately 2000, however, the role of OMBP has come under increasing scrutiny. Aside from patient complaints of OMBP often not being well tolerated and potential issues with dehydration and electrolyte imbalances, investigators have perhaps more importantly questioned whether OMBP is as effective as traditionally thought in terms of reducing surgical site infection (SSI) rates.

Multiple randomized clinical trials over the last two decades failed to show any benefit from OMBP in terms of overall infectious complications and more specifically anastomotic leak rates [2–5]. The largest study evaluating 1343 patients randomized to OMBP or no OMBP found no significant differences in overall complications (24.5% OMBP vs. 23.7% no OMBP) nor in general infectious complications (7.9% OMBP vs. 6.8% no OMBP) [5]. Several meta-analyses have corroborated these findings (see Table 1.1) [6–8]. Indeed, the most recent Cochrane review in 2011, evaluating 18 trials, found no significant difference in wound infection, anastomotic leak rates, noninfectious complications, or mortality [9]. This has led to both European and Canadian surgical societies to recommend against routine

N. Shah (✉)
Rhode Island Hospital, Providence, RI, USA
e-mail: nshah@usasurg.org

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Table 1.1 Pairwise meta-analysis results for the comparison of OMBP versus enema or no preparation

Outcome	Comparison	*N* studies (*N* events/*N* patients, per group)	OR (95% Cl)	Between-study variance (95% Crl)
All-cause mortality	OMBP ± enema vs enema/no prep	14 (45/2550 vs 44/2544)	1.17 (0.67–2.67)	0.12 (0.00–1.99)
	OMBP ± enema vs no prep	10 (38/2024 vs 40/2014)	1.09 (0.57–2.99)	0.17 (0.00–2.61)
	OMBP ± enema vs enema	4 (7/526 vs 4/530)	1.99 (0.27–18.45)	0.82 (0.00–3.76)
Anastomotic leakage	OMBP ± enema vs enema/no prep	16 (126/2702 vs 124/2680)	1.08 (0.79–1.63)	0.08 (0.00–0.72)
	OMBP ± enema vs no prep	12 (102/2176 vs 103/2150)	1.06 (0.73–1.73)	0.09 (0.00–0.95)
	OMBP ± enema vs enema	4 (24/526 vs 21/530)	1.24 (0.38–4.72)	0.61 (0.00–3.59)
Wound infection	OMBP ± enema vs enema/no prep	16 (266/2612 vs 239/2603)	1.19(0.93–1.63)	0.04 (0.00–0.41)
	OMBP ± enema vs no prep	12 (218/2086 vs 190/2073)	1.27 (0.95–1.88)	0.05 (0.00–0.50)
	OMBP ± enema vs enema	4 (48/526 vs 49/530)	1.04 (0.37–3.34)	0.52 (0.00–3.46)
Peritonitis/ intra-abdominal abscess	OMBP ± enema vs enema/no prep	14 (51/2381 vs 70/2362)	0.84 (0.50–1.66)	0.25 (0.00–1.77)
	OMBP ± enema vs no prep	10 (45/1855 vs 64/1832)	0.84 (0.45–2.00)	0.38 (0.00–2.74)
	OMBP ± enema vs enema	4 (6/526 vs 6/530)	0.99 (0.21–4.68)	0.42 (0.00–3.51)
Reoperation	OMBP ± enema vs enema/no prep	8 (124/1967 vs 119/1945)	1.14 (0.57–2.65)	0.38 (0.00–3.23)
	OMBP ± enema vs no prep	6 (117/1742 vs 111/1723)	1.15 (0.73–2.50)	0.09 (0.00–1.82)
	OMBP ± enema vs enema	2 (7/225 vs 8/222)	0.50 (0.03–6.12)	2.49 (0.27–3.93)
SSI	OMBP ± enema vs enema/no prep	7 (206/1279 vs 197/1230)	1.19 (0.56–2.63)	0.64 (0.11–2.91)
	OMBP ± enema vs no prep	5 (173/1087 vs 171/1040)	1.10 (0.41–3.05)	0.76 (0.10–3.39)
	OMBP ± enema vs enema	2 (33/192 vs 26/190)	1.50 (0.24–10.42)	1.20 (0.02–3.79)

OR values <1 indicate that events are less common among OMBP-treated groups (ie, that OMBP is beneficial). *Crl* credibility interval, *no prep* no OMBP and no enema, *OMBP* oral mechanical bowel preparation, *SSI* surgical site infection

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use of OMBP undergoing elective colon surgery [10, 11]. The Canadian Society did however deem the evidence insufficient to support or refute use of OMBP in elective rectal cancer surgery.

We recently undertook a systematic review of these studies (Fig. 1.1) [8]. We found that these studies used a variety of OMBP regimens, and this lack of standardization might have affected the validity of the findings. Furthermore, although almost all of the trials reported adjunct use of parenteral antibiotics perioperatively, the vast majority omitted oral nonabsorbable antibiotics. The role of gut decontamination with oral antibiotics will be expanded on below. In addition, we found there was some indication for between-study heterogeneity, particularly in the comparison of OMBP with or without enema versus enema alone for rectal surgery (Table 1.2). Details on the surgical indications (cancer vs. diverticular disease vs. inflammatory bowel disease), surgical approach (laparoscopic vs. open surgery), as well as operation types were generally poorly reported. This is relevant as numerous studies have recently found that surgical site infection (SSI) in colorectal surgery is influenced by primary disease diagnosis as well as the use of laparoscopy. The Mayo Clinic group noted that operations for diverticular disease were associated with more superficial SSI, whereas ulcerative colitis patients had more deep/organ space SSIs.

The benefits of laparoscopic surgery in reducing SSI have been clearly demonstrated. In a prospective study from Hong Kong of over 1000 patients, the rate of SSI was significantly higher following open surgery (5.7% open vs. 2.7% laparoscopic, $p < 0.05$) [12]. This benefit is further amplified in our growing obese patient population. It is uncertain whether the results of OMBP trials involving predominantly open surgical procedures can be extended to laparoscopic operations, particularly as from a technical standpoint prepped bowel may be easier to manipulate during a laparoscopic resection.

A note should be made regarding elective rectal surgery. It has been well documented that the risk of anastomotic leaks is greater in this setting compared to colon surgery, particularly when associated with low extraperitoneal anastomoses [13]. Indeed, a recent observational analysis involving patients undergoing resection surgery for colorectal surgery found that rectal resections were independently associated with an increased likelihood of both superficial and deep/organ space SSI [14]. With respect to stratification by surgical site in the trials we analyzed, only one randomized trial has been published exclusively enrolling patients undergoing rectal surgery, and only two studies looked specifically at left-sided colorectal operations. The GRECCAR III randomized trial from France showed a significant increase in infectious complications in the absence of OMBP (34% no OMBP vs. 16% OMBP, $p = 0.005$) but no difference in anastomotic leak rates, major morbidity, nor mortality rate [15]. A subgroup analysis of a large multicenter randomized OMBP trial examining outcomes of 449 patients who had undergone a low anterior resection with a primary anastomosis also revealed no difference in anastomotic leak rates, irrespective of whether a diverting ileostomy was created [16]. Furthermore, a recent meta-analysis also confirmed that OMBP had no impact on SSI, anastomotic leak rates, nor overall morbidity and mortality in patients

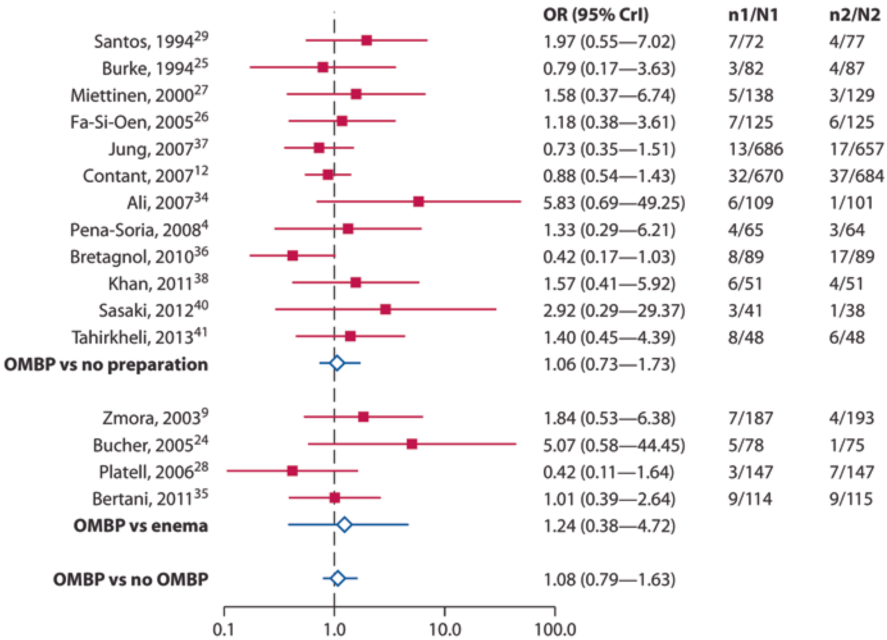

Fig. 1.1 Anastomotic leakage meta-analysis results for studies comparing OMBP (with or without enema) versus enema or no preparation. Reprinted with permission from [8]

Table 1.2 Meta-regression results for studies comparing OMBP (with or without enema) versus enema or no preparation

Outcome	Potential modifier	rOR (95% Crl)
All-cause mortality	ROB for randomized sequence generation (low vs moderate/high/unclear)	0.33 (0.07–1.40)
	ROB for allocation concealment (low vs moderate/high/unclear)	0.88 (0.23–4.39)
	Year of publication	0.98 (0.90–1.04)
Anastomotic leakage	ROB for randomized sequence generation (low vs moderate/high/unclear)	0.72 (0.35–1.56)
	ROB for allocation concealment (low vs moderate/high/unclear)	0.45 (0.23–0.86)[a]
	Year of publication	0.98 (0.91–1.05)
Wound infection	ROB for randomized sequence generation (low vs moderate/high/unclear)	0.90 (0.51–1.72)
	ROB for allocation concealment (low vs moderate/high/unclear)	0.64 (0.38–1.08)
	Year of publication	1.00 (0.97–1.03)

[a]Results are suggestive of an association
Crl credibility interval, *ROB* risk of bias, *rOR* relative OR, *SSI* surgical site infection
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undergoing a proctectomy [17]. In our recent review regarding OMBP and rectal surgery, we found that although there was no evidence of any beneficial effect of OMBP, this summary estimate was imprecise. The small number of studies in this setting was often underpowered with heterogeneous subgroup definitions, with the level of the anastomosis and use of protective diverting stomas often unclear [8].

Despite this ostensibly compelling data on the lack of its efficacy, the vast majority of US surgeons performing colorectal surgery still currently employ OMBP. Indeed, this ongoing debate has been revisited over the last couple of years, with the results of several large US studies seemingly swinging the pendulum back in favor of OMBP. Several recent National Surgical Quality Improvement Program (NSQIP) retrospective studies concluded that OMBP combined with oral antibiotics resulted in reduced SSI as well anastomotic leak rates after elective colorectal surgery [18, 19]. In the largest study by Kiran et al., over 8000 patients were divided into three groups: no OMBP (27%), OMBP but no oral antibiotics (45%), and OMBP with oral antibiotics (28%). On multivariate analysis, OMBP with oral antibiotics, but not without, was independently associated with lower SSI, reduced anastomotic leak rates, as well as shorter postoperative ileus. The authors acknowledged that the no OMBP group did have more patients with sepsis, ascites, steroid use, disseminated cancer, and ASA class greater than 3, as well as fewer laparoscopic resections. Although their multivariate analysis tried to account for these differences, it is unclear to what extent these comorbidities may have contributed to the poorer results in the no OMBP group [18].

If there is some validity to these NSQIP reports, however, how do we reconcile these seemingly discrepant findings with those of the many randomized trials previously discussed? A closer examination of the OMBP literature suggests the role oral antibiotics may play in determining outcomes. The use of oral antibiotics to lower the bacterial load in the colon was popularized following the seminal study by Nichols in 1972 which demonstrated a reduction in SSIs in patients treated with a combination of OMBP and an oral neomycin-erythromycin regimen. Although their use gradually declined over the next couple of decades, there has been renewed interest in the value of oral antibiotics recently. A double-blind, randomized controlled trial by Lewis revealed that patients receiving both oral and intravenous antibiotics had a marked decrease in SSI (RR = 0.29, $p < 0.01$) and a much lower incidence of colonic bacteria in the surgical wound at the end of the case, compared to those receiving intravenous antibiotics alone, both groups having undergone OMBP [20]. In two more recent retrospective reviews from the Veterans Affairs (VA) NSQIP database and from the Michigan Surgical Collaborative, patients receiving both oral and parenteral antibiotics had dramatically lower SSI rates compared to patients receiving parenteral antibiotics alone [21, 22]. A closer breakdown of the VA study of over 9900 patients undergoing colorectal surgery showed that patients receiving preoperative oral antibiotics alone had similar SSI rates to those receiving oral antibiotics plus OMBP (8.3 vs. 9.2%). In addition, those patients receiving no OMBP had similar SSI rates compared to those receiving OMBP alone without oral antibiotics (18% vs. 20%) [21]. Moreover, in another NSQIP analysis of over 8400 colorectal operations, Morris reported that oral antibiotics reduced SSI rates compared to the no OMBP and OMBP alone groups (6.5% vs. 14.9%, vs.12.0%, respectively, $p < 0.001$) and resulted in lower anastomotic leak rates [19]. Similar to the VA study, there was no significant difference in SSI rates in the oral antibiotic plus OMBP group to those patients given oral antibiotics alone, though the latter group constituted only 8% of the patients. Putting these results together, it is evident that gut decontamination with oral nonabsorbable antibiotics may play a significant role in reducing infectious complications in colorectal surgery. Yet in our review of the many trials comparing the efficacy of OMBP to no bowel preparation, although we found no evidence of any benefit with OMBP use, we only noted three studies in which oral antibiotics were administered. Furthermore, although the traditional, intuitive opinion has been that oral antibiotics can only be administered after completion of a mechanical bowel preparation, the VA NSQIP and Morris studies suggest that even without an OMBP the benefits of oral antibiotics in reduction of SSI may persist.

Conclusion

Although we found no definitive evidence that OMBP is beneficial in elective colorectal surgery, the evidence on which this assumption is based was weak and of low quality. Moreover, many of these published studies do not reflect changes in the current practice of colorectal surgery, such as the increased popularity of laparoscopic surgery and enhanced recovery pathways. We propose there is an important need for a large randomized controlled trial examining all combinations of using or withholding OMBP, with and without oral antibiotics. Such a study should not be difficult due to the large volume of elective colorectal operations performed annually. A noninferiority design could be used to examine whether omission of OMBP does not worsen clinical outcomes, while a factorial design could readily determine the interaction between OMBP and oral antibiotics with a careful breakdown of anatomic location (colon vs. rectum) and the approach used (open vs. laparoscopic).

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Practice Guidelines and Future Directions of Bowel Preparation: Science and History

2

Megan Turner, Zhifei Sun, and John Migaly

Introduction

Intestinal antisepsis has been a principle of health intervention since antiquity [1–3]. Bowel preparation and antisepsis have become a surgical interest with Jacques Lisfranc successfully performing the first perineal resection in 1826 and John Miles performing the first abdominoperineal resection in 1908 [4]. As sophistication of operative techniques, pharmacology, and perioperative care increased in the 1900s, the use of evidence-based practices for bowel preparation became an effective preoperative intervention for decreasing postoperative complications. This review will present basic scientific principles and key historical developments in the use of preoperative bowel preparation. Descriptions of combined mechanical, oral, and parenteral preparation are to follow, concluding with the current best practice guidelines and queries for future areas of study.

Basic Scientific Principles

At baseline, the colon has a high bacterial load, with up to 10^7 aerobic colony-forming units (CFU) per milliliter of irrigation and 10^8 anaerobic CFU per milliliter of irrigation [5]. Wound studies following colonic operations show a predominance of mixed aerobic-anaerobic growth, largely composed of *Bacteroides fragilis* and *Escherichia coli* [5]. In the early 1900s, nearly 80% of postoperative patients suffered from infectious complications with a 20% mortality [4]. Postoperative infections were attributed to colonic bacteria introduced into the surgical site following resection with gross or microscopic spillage, not introduced from the skin flora or

M. Turner (✉) • Z. Sun • J. Migaly
Department of Surgery, Duke University Medical Center, Durham, NC, USA
e-mail: megan.turner@dm.duke.edu; zhifei.sun@dm.duke.edu; John.Migaly@dm.duke.edu

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surgical team. In an attempt to decrease infectious morbidity, methods to decrease bacterial load were developed including mechanical bowel preparation and the use of antibiotics.

Mechanical preparations of bulking agents were popularized to facilitate evacuating the entirety of the intestinal tract, frequently followed by enemas to ensure complete cleanliness. The dogma of early intestinal surgery was that no anastomosis should be made with residual fecal contents present.

In the 1940s, nonabsorbable sulfonamides were tested for impact on colonic bacterial counts. Little effect on postoperative infectious outcomes was found with sulfonamide use given the narrow spectrum of activity, bacteriostatic nature, and the associated multiday mechanical bowel preparation [6–8]. Sensitivity studies that followed examined single-agent antibiotic preparations compared to multiple-agent antibiotic preparations. Single-agent therapies were found to be inferior to combination therapies in the reduction of colonic bacteria and subsequent postoperative sepsis [9, 10]. A decrease in colonic bacterial counts of up to 10^5 was observed in all major colonic bacterial groups following oral combination antimicrobial therapy [5].

Early studies examined the emergence of single organism overgrowth and bacterial resistance in fecal flora following antimicrobial therapy. Single-agent preparations were associated with increased growth of isolated organisms, leading to diarrhea and pseudomembranous colitis [6, 11]. The use of combination therapy prevented the emergence of overgrowth, and resistant strains were avoided [5, 12].

History of Bowel Preparation

1860s–Early1900s

In the late 1860s, the quest for medical antisepsis began with the established relationship between bacteria and disease. Halsted is known for his work in antiseptic surgical technique in the 1890s, which was not widely adopted until well into the twentieth century. In parallel with development of techniques for aerobic and anaerobic cell culture came clinical studies evaluating the efficacy of mechanical bowel preparation on reducing bacterial burden. Historically, preoperative bowel preparation was guided by the principle of complete colonic emptying by starvation and purgation. Surgeons of the 1900s used bulking agents and stimulants to empty the bowel of its contents [13]. Mechanical bulking agents, such as vegetable matter, increased the volume of stool and allowed easier passage. Castor oil (a stimulant of peristalsis through its conversion to ricinoleic acid in the duodenum) was a choice purgative. It was believed clearing the bowel of fecal material would decrease the total bacterial burden, decreasing the risk of infection.

Surgical experiments at this time were performed primarily in animals and focused on the integrity of intestinal anastomoses, specifically evaluating dehiscence and leak [14]. The leading theory was that an unprepared bowel would be unable to heal an intestinal anastomosis. However, as early as the 1920s, the doctrine of complete bowel emptying prior to anastomosis formation was challenged with the advent of antibiotics [15]. The discovery of nonabsorbable enteral antibiotics led to experimentation of intestinal antisepsis in both animals and humans.

1940s–1970s

With the introduction of antibiotics, surgeons began to use enteral antibiotic formulations in addition to mechanical preparation to reduce postoperative morbidity. Early studies examined the impact of preoperative enteral preparations on surgical site infection, correlating cultures from colonic specimens and subsequent wound infections [9, 10, 16]. Through these studies, it was apparent that appropriate prophylaxis required coverage of both aerobes and anaerobes to obtain clinical effectiveness [11, 17, 18]. Given the bacteriostatic nature of the available antibiotics, they were administered in combination with mechanical bowel preparations over several days preoperatively. Nichol's 1973 landmark prospective randomized control trial, and subsequent retrospective analysis, compared mechanical preparation to mechanical preparation plus nonabsorbable enteral antibiotics. A dramatic decrease in surgical site infection with combination therapy was observed. Thus, the combination was termed the "Nichols prep" and has continued use in modern practice [19].

Similarly, the 1977 prospective randomized control trial by Clarke et al. showed a decrease in postoperative septic complications in patients who received both enteral antibiotics and mechanical bowel preparation [20]. Subsequent trials provided additional evidence that enteral antibiotics improved outcomes with decreased anastomotic dehiscence and surgical site infections independent of mechanical bowel preparation [5, 21]. Even in these early studies, the authors have suggested that mechanical preparation alone will become obsolete. Studies in pathophysiology showed that intestinal anastomoses without preoperative antibiotic therapy were healed by secondary intention as seen with superficial contaminated wounds, whereas anastomoses protected by enteral antibiotics were healed by primary intention [6, 12].

As a result of the trials by Nichols and Clark, the combination of enteral antibiotics and mechanical preparation was widely implemented and based in substantial evidence. By the end of the 1970s, it was the standard of care for elective colorectal procedures. The availability of broad-spectrum parenteral antibiotics became the next frontier in battling postoperative complications for colorectal surgery.

1980s–1990s

Combination of mechanical and enteral antibiotic bowel preparation was well established in the 1980s [22]. However, the role of parenteral antibiotics was unclear. Surgeons sought to maintain low rates of postoperative complications while streamlining preoperative antisepsis interventions. Burke et al. describe the use of parenteral antibiotics in patients randomized to a mechanical preparation compared to no preparation. No difference in anastomotic dehiscence or wound infections was found [23]. Petrelli et al. utilized mechanical preparation and oral antibiotics and randomized their patients to receive parenteral antibiotics. Their findings concluded that parenteral antibiotics provided no additional benefit, with equal distribution of anastomotic and infectious complications [24]. Conversely, a large prospective randomized trial by Schoetz et al. showed dramatic improvement in infectious complications in patients who received parenteral antibiotics in addition to oral antibiotics and mechanical preparation [25]. Despite early conflicting evidence, by the late 1990s, the consensus of practicing colorectal surgeons was the use of mechanical preparation and parenteral and enteral antibiotics in preparation for elective colorectal surgery [26, 27].

2000–2010

Following over 100 years of strict adherence to elective intestinal anastomoses being performed in mechanically cleansed bowels, data from trauma surgery in the early 2000s challenged these practices [28–30]. Curran et al. performed a meta-analysis of 35 studies including 5400 penetrating colon injuries to better define the consequences of primary repair in the setting of trauma [29]. Their findings were a low rate of anastomotic leak, concluding colonic injury may be managed by primary repair in select circumstances. This analysis was further supported by a subsequent prospective multicenter trial by Demetriades et al. which compared outcomes between patients with penetrating colon injury who underwent primary repair with and without diversion [30]. They found no difference in intra-abdominal complications between the two groups accumulating evidence for the safety of performing anastomoses in an un-prepped colon. This data was extrapolated to elective colorectal surgery as evidence for the possibility of a safe anastomosis without mechanical preparation.

Randomized trials during this same time period examined the need for mechanical preparation with the use of parenteral antibiotics in elective colorectal surgery. Zmora et al. randomized 380 patients to either mechanical bowel preparation or no preparation for elective colon resection. All patients received enteral and parenteral antibiotics. They found no difference in infectious or anastomotic complications leading to the conclusion that anastomoses can be safely created in a nonmechanically prepped bowel with enteral and parenteral antibiotics [31]. This was complemented by a larger multicenter trial by Contant et al. randomizing 1400 patients to parenteral antibiotics with or without mechanical preparation, and they found no difference in anastomotic integrity [32]. In 2002, Lewis et al. performed a randomized, placebo-controlled prospective trial examining the impact of combination mechanical, enteral, and parenteral antibiotic preparation compared to mechanical and parenteral antibiotics alone. They concluded the combination of systemic and enteral antibiotic prophylaxis was superior to systemic antibiotics alone [33]. Additionally, their meta-analysis of studies through the 1990s corroborated their conclusions.

The Cochrane Review guidelines of 2009 recommended enteral and parenteral antibiotics prior to elective colorectal surgery with a reduction in infectious complications by 75% [34]. In their meta-analysis, improved surgical site infectious outcomes with combination of enteral and parenteral antibiotics over either therapy alone were observed. No outcome differences were seen between different regimens of antibiotics, providing the patients had adequate aerobic and anaerobic coverage. Length of antibiotic therapy did not lead to a difference in outcomes, but concerns arose regarding the development of resistant organisms and *Clostridium difficile* (*C. diff*) infection with prolonged use.

The association between antibiotic prophylaxis for colorectal surgery and *C. diff* has garnered limited enthusiasm for newer studies despite worse outcome implications for postoperative patients infected with *C. diff.* In 2005 Wren et al. retrospectively examined the impact of enteral antibiotics, in addition to parenteral antibiotics and mechanical preparation, finding higher incidences of *C. diff* infections in those receiving enteral prophylaxis [35]. Their cohort did not have differences in surgical site infection or anastomotic breakdown. A larger follow-up study was performed in 2011 by the Michigan Surgical Quality Colectomy Project, which did not find a difference in rates of *C. diff* among patients who underwent mechanical bowel preparations versus preparations with enteral antibiotics [36]. Based on the clear benefit of enteral antibiotic use on overall outcomes for elective colorectal resections, the use of enteral antibiotics continues to be the standard of care. Minimizing the incidence of *C. diff* infection rates remains a challenge in the postoperative period.

Best Practice Guidelines

Despite the large body of data surrounding the use of various preparations in combination, in 2011, Englesbe et al. published the first study to compare patients receiving parenteral antibiotic prophylaxis without mechanical preparation or enteral antibiotics to those receiving combined mechanical preparation and enteral and parenteral antibiotics. Using the Michigan Surgical Quality Collaborative-Colectomy Best Practices Project database, patients undergoing elective colon resections were evaluated in propensity-matched groups to evaluate outcomes between the un-prepped cohort and the combination prepped cohort [37]. Their primary outcomes evaluated surgical site infection, *C. diff* colitis, prolonged ileus, as well as National Surgical Quality Improvement Project (NSQIP) outcomes. In their unadjusted analysis, no differences were observed in rates of surgical site infection with or without mechanical preparation. However, among propensity-matched patients, significant outcome differences were seen; specifically, surgical site infections were lower with enteral antibiotic use. Correspondingly, superficial wound infections and organ space surgical site infections were lower with enteral antibiotic use. Additionally, the use of enteral antibiotics was associated with reduced rates of prolonged ileus, without an increase in the risk for *C. diff.*

In 2014, Nelson et al. provided recommendations in an updated Cochrane Review; the quality of the existing evidence was such that the recommendations are unlikely to change significantly with future studies. No benefit was found with mechanical bowel preparation alone, and there was significant benefit to combined preparation of mechanical, enteral, and parenteral antibiotic prophylaxis. While there was robust data that no benefit exists with mechanical preparation alone, given the support for nonabsorbable enteral antibiotic use, many surgeons continued to use mechanical preparation as no studies determined the efficacy of enteral antibiotics in an un-prepped colon [38].

Our group addressed the concerns outlined above with a retrospective study of the National Surgical Quality Improvement Project data to conclude that combined mechanical, enteral, and parental antibiotic preparations prior to elective colorectal surgery had improved outcomes [39]. Specifically, the use of enteral antibiotics in a mechanically prepped colon and an un-prepped colon is addressed. The primary outcomes measured were incisional surgical site infection, anastomotic leak, and mortality. We found that the combination of mechanical preparation and enteral and parenteral antibiotics had lower incidence of incisional surgical site infection, lower incidence of anastomotic leak, shorter postoperative length of stay, and lower readmission rates compared to patients with no preparation [39]. In general, there was no significant difference in outcomes between patients who received mechanical preparations and parenteral antibiotics or enteral and parenteral antibiotic preparations without mechanical preparation and patients who received parenteral antibiotics alone. The improved effect of enteral antibiotics in combination with mechanical preparation is attributed to decreases in fecal bulk increasing the delivery of the antibiotics to the colonic mucosa.

Future Directions

In the last decade, our understanding of commensal bacteria on human immunology and tissue healing has led to reevaluation of antibiotic prescriptive practices. This increase in knowledge spurred the National Institute of Health to sponsor the Human Microbiome Project Roadmap Initiative to catalogue the human microbiome to better characterize the impact of these organisms on human health and disease. With regard to colorectal surgery, the Nichols preparation of preoperative, nonabsorbable, enteral antibiotics is based on historic fecal culture data. These studies have not been repeated with newer techniques, namely, genomic sequencing; thus, there is an incomplete understanding of the bacterial community of the colon. There is strong evidence for the use of broad-spectrum, nonabsorbable, preoperative antibiotics in the prevention of anastomotic leak; however, given the incomplete catalog of bacteria at the site, the mechanism of this phenomenon is incompletely understood. The newest data regarding anastomotic healing examines the impact of bacteria on induction of human immune factors both systemically and at the site of the anastomosis [40, 41]. Additionally, under postoperative stress, pathogenic bacterial factors are produced with unknown consequences on tissue healing [40, 42, 43].

As the impact of the bacterial communities within the colon is further understood, preoperative enteral antibiotic regimens will need to be developed with increasing specificity to optimize outcomes following resection and anastomosis.

The findings from the large-scale retrospective studies of our group and Morris et al. elucidate the need for a prospective randomized trial to increase the robustness of data surrounding the benefit of combined mechanical preparation with enteral and parenteral antibiotics [44]. The impact of combined preparations on *Clostridium difficile* infections and outcomes has yet to be fully examined and will likely be impacted by the choice and timing of antibiotic preparations. Surgeon prescriptive practices for preoperative antibiotic prophylaxis will need to be responsive to discoveries that result from the Human Microbiome Project. Additionally, in retrospective studies, significant variability is observed in prescribed preparations in current practice [39]. Examination of variability and adherence to best practice guidelines are important in improving postoperative morbidity metrics on a national level.

Conclusions

The use of combined enteral antibiotics, mechanical preparation, and parenteral antibiotic prophylaxis, while arduous, leads to improved postoperative outcomes compared to streamlined preparations in elective colorectal surgery. Further directions of study include optimization of antibiotic timing and comprehensive characterization of colonic bacterial communities. Prescription variability and adherence to best practice guidelines remain as challenges in moving forward.

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