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ARTICLE

Unintended consequences of antibiotic practices: the relationship between bowel preparation, prolonged prophylaxis, and ileus after radical cystectomy

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Objectives: *Postoperative ileus (POI) after radical cystectomy (RC) is a common complication that carries significant morbidity. Prolonged antibiotic usage has been associated with an elevated risk of POI. The American Urological Association guidelines recommend that only a single dose of peri-procedural antibiotic prophylaxis is sufficient. This study aims to evaluate the association between oral antibiotic bowel preparation (ABP) and prolonged surgical antibiotic prophylaxis (SAP) (>24 h) with postoperative ileus (POI) following radical cystectomy (RC).*

Materials and Methods: *A retrospective cohort study using the American College of Surgeons National Surgical Quality Improvement Program procedure-targeted RC dataset was performed. Patients with clinical indications for extended antibiotic use were excluded. POI was defined as nil per os status, or nasogastric tube use beyond postoperative day three, or reinstitution of either on or after day four. Clinical, perioperative and oncological characteristics were compared between patients to identify factors associated with POI.*

Results: *Among 5098 patients undergoing RC, the incidence of POI was 12.4%. A small fraction of patients received ABP (6.5%), mechanical bowel preparation (MBP) was given to 22.1% of patients, and 23.4% patients received SAP for more than 24 h. On univariate analysis, ABP (Odds ratio (OR) 1.711), open surgical approach (OR 1.542), prior pelvic radiotherapy (OR 1.515), age > 65 years (OR 1.386), SAP > 24 h (OR 1.378), and receipt of chemotherapy within 90 days (OR 1.220) were associated with POI. However, on multivariate analysis, only oral ABP (OR 1.692, $p = 0.009$), SAP > 24 h (OR 1.460, $p = 0.04$), and age > 65 years (OR 1.361, $p = 0.031$) remained independently significant.*

Conclusions: *Oral ABP and prolonged SAP are associated with increased risk of POI following RC. These findings underscore the importance of adherence to evidence-based perioperative protocols and antibiotic stewardship to improve postoperative outcomes in urologic oncology.*

Key Words: Antibiotic stewardship, antibiotic use, ileus, paralytic ileus, radical cystectomy

Introduction

Bladder cancer and its definitive surgical treatment, radical cystectomy (RC), are associated with substantial morbidity and healthcare resource utilization. Globally, over 613,791 individuals were diagnosed with bladder cancer in 2022 and accounted for 220,349 deaths in the same year.[1,2] Radical cystectomy, irrespective of surgical approach, carries a high complication rate—reported in 60%–80% of patients.[3] These complications often contribute to prolonged hospitalization, which in turn is linked to increased healthcare costs, higher risk of additional complications, and increased mortality. The economic

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burden is considerable, with median per-patient costs reaching approximately $70,761 within 90 days of surgery.[4,5]

A major determinant of prolonged hospitalization following RC is postoperative ileus (POI), which affects approximately 23.5% of patients.[6,7] POI is clinically defined as intolerance to oral intake in the absence of mechanical obstruction, occurring on or after postoperative day three, and may necessitate nasogastric decompression.[8] This condition is associated with increased length of stay, higher rates of readmission and reoperation, and elevated postoperative mortality. Contributing risk factors include advanced age, elevated body mass index, and neoadjuvant chemotherapy.[9–13] Given its clinical and economic impact, the prevention of POI remains a central objective in Enhanced Recovery After Surgery (ERAS) protocols.[14]

Prolonged antibiotic usage has been associated with an elevated risk of postoperative ileus (POI).[15] In patients undergoing radical cystectomy (RC), bowel preparation regimens are commonly employed and typically consist of either oral antibiotic bowel preparation (ABP), or mechanical bowel preparation (MBP) using laxatives, or a combination of both.[16–19] However, the cumulative antibiotic exposure is further exacerbated by the administration of surgical antibiotic prophylaxis immediately prior to surgery. The American Urological Association (AUA) guidelines recommend a single preoperative dose of antibiotic prophylaxis for RC, emphasizing that the prophylactic benefit is confined to the first 24 h postoperatively.[20] Despite these recommendations, substantial deviations from SAP guidelines persist. In a large national cohort study, Branch-Elliman et al. found that 26.9% of patients across various surgical specialties received antibiotic prophylaxis for durations exceeding 24 h, contrary to established guidelines.[21]

Given the potential adverse effects associated with prolonged antibiotic use, including the development of POI, this study aimed to investigate the relationship between antibiotic practices and postoperative gastrointestinal outcomes in RC. Utilizing data from the American College of Surgeons National Surgical Quality Improvement Program (ACS NSQIP) procedure-targeted cystectomy database from 2019 to 2022, we sought to: 1. determine the contemporary incidence of POI following RC; 2. compare clinical and perioperative characteristics between patients who developed POI and those who did not; and 3. identify independent predictors of POI with a particular emphasis on the roles of ABP and extended SAP (>24 h). The findings from this investigation are intended to inform evidence-based refinements to perioperative care pathways and support efforts to improve surgical outcomes for patients undergoing RC.

Materials and Methods

Patients and databases

We conducted a retrospective cohort study using ACS-NSQIP procedure targeted cystectomy databases from 2019–2022 to identify patients who underwent cystectomy. The American College of Surgeons National Surgical Quality Improvement Program and the hospitals participating in the ACS NSQIP are the source of the data used herein; they have not verified and are not responsible for the statistical validity of the data analysis or the conclusions derived by the authors. The study was deemed exempt from Institutional Ethics Committee approval and informed consent process due to the use of de-identified data.

From the ACS NSQIP cystectomy-targeted database, all the patients aged 18 years and above were included. A total of 5098 patients who underwent RC were identified for inclusion in the study after excluding individuals aged less than 18 years and those with clinically justified indications for extended postoperative antibiotic therapy. These exclusions included patients with surgical site infections, wound dehiscence, urinary tract infections, pneumonia, rectal injury, anastomotic leak, sepsis, septic shock, or those who underwent secondary procedures.

Outcomes

The primary outcome of interest was the occurrence of POI within 30 days of RC. POI was defined as the persistence of *nil per os* (NPO) status or the use of a nasogastric tube beyond postoperative day three, as well as any reinstitution of NPO status or reinsertion of a nasogastric tube on or after postoperative day four within the immediate 30-day postoperative period. The baseline demographic parameters of those patients who developed POI after RC and those who did not develop POI were compared. In general, ABP was defined as the use of oral antibiotics such as neomycin, erythromycin or metronidazole to reduce the colonic bacterial flora load and MBP included laxatives like polyethylene glycol to reduce colonic stool load. However, the data was limited by lack of specific details regarding antibiotic and laxative choice.

TABLE 1. **Co-variates and factors utilized in the study**

Demographic characteristics:
Age > 65 years
Comorbid conditions:
History of smoking
Chronic obstructive pulmonary disease (COPD)
Diabetes
Congestive heart failure
Hypertension
Dependent functional status
Chemotherapy within ninety days
Prior pelvic radiotherapy
Prior pelvic surgery
Operative characteristics:
Open Surgical Approach
Surgical antibiotic prophylaxis > 24 h
Drain placement
Bowel prophylaxis strategy:
Oral antibiotic bowel preparation (ABP)
Mechanical bowel preparation (MBP)

Statistical analysis

Continuous data were reported as means with standard deviations and compared using *t*-tests and categorical data were reported as percentages and compared using Chi-square statistics. A univariate and multivariate logistic regression analysis was conducted for development of POI using co-variates listed in Table 1. All models were tested for goodness-of-fit using Hosmer-Lemeshow test, and for multicollinearity using variance inflation factors. A *p*-value of less than 0.05 was considered statistically significant. All statistical analyses were conducted using SPSS Version 30 software by IBM Corp, Armonk, New York, USA.

Results

The overall incidence of postoperative ileus (POI) within 30 days of RC was 12.4%. Patients who developed POI experienced significantly longer hospital stays compared to those without POI (mean 9.0 vs. 6.2 days, $p < 0.001$).

Baseline demographic, clinical, perioperative, and oncologic characteristics were compared between the two cohorts, as summarized in Table 2. No statistically significant differences were observed in mean age or body mass index (BMI). However, several variables were significantly more prevalent among patients who developed POI, including prior pelvic radiotherapy (11.6% vs. 8.0%, $p = 0.002$), chronic obstructive pulmonary disease (8.0% vs. 5.8%, $p = 0.032$), hypertension (63.5% vs. 58.3%, $p = 0.012$), open surgical approach (77.8% vs. 67.9%, $p < 0.001$), use of oral antibiotic bowel preparation (ABP) (8.8% vs. 6.2%, $p = 0.038$), and administration of surgical antibiotic prophylaxis for more than 24 h (25.0% vs. 23.2%, $p = 0.024$).

Additionally, the mean operative time was longer in patients who developed POI (332.08 vs. 326.21 min, $p < 0.001$). Interestingly, patients receiving neoadjuvant chemotherapy within 90 days had lower rates of POI (34.4% vs. 39.0%, $p = 0.026$). No significant differences were observed between the cohorts in terms of tumor stage or surgical drain placement practices.

Table 3 summarizes the logistic regression analysis for factors associated with POI. On univariate analysis, use of ABP (odds ratio (OR) 1.711, 95% confidence interval (CI) 1.155–2.536, $p = 0.007$), open approach (OR 1.542, 95% CI 1.167–2.038, $p = 0.002$), prior pelvic radiotherapy (OR 1.515, 95% CI 1.161–1.978, $p = 0.002$), age more than 65 years (OR 1.386, 95% CI 1.049–1.830, $p = 0.022$), SAP for more than 24 h (OR 1.378, 95% CI 1.012–1.877, $p = 0.042$), and receipt of chemotherapy within 90 days (OR 1.220, 95% CI 1.025–1.452, $p = 0.026$) were associated with increased odds of POI. On multivariate logistic regression, only three variables remained independently associated with the development of POI: receipt of oral ABP (OR 1.692, 95% CI 1.140–2.511, $p = 0.009$), administration of SAP for more than 24 h (OR 1.460, 95% CI 1.280–2.176, $p = 0.04$), and age greater than 65 years (OR 1.361, 95% CI 1.029–1.800, $p = 0.031$).

Discussion

This large, nationwide retrospective cohort study provides an updated estimate of the incidence of postoperative ileus (POI) following radical cystectomy (RC), along with a comprehensive characterization of the demographic, clinical, perioperative, and oncologic profiles of affected patients. Importantly, our findings demonstrate a significant association between the use of oral antibiotic bowel preparation (ABP), prolonged surgical antibiotic prophylaxis, and the development of POI.

POI remains a common and clinically significant complication following major abdominal and pelvic surgeries, including RC. Prior studies and systematic reviews have reported a wide range in rates of POI after RC, varying from 1.58% to 26.9%.[3,22–24]

TABLE 2. **Demographic, clinical, perioperative, and oncologic characteristics of the cohorts of patients who developed POI and those who did not**

	Patients without POI (n = 4465)	Patients with POI (n = 633)	*p*-value
Age, in years (Mean)	69.81	70.96	0.487
BMI, in kg/m² (Mean)	29.18	28.99	0.943
Comorbid Conditions			
ASA 3/4/5 (%)	79.8%	81.6%	0.311
Hx diabetes (%)	19.0%	17.8%	0.452
Hx severe COPD (%)	5.8%	8.0%	0.032
Hx CHF (%)	2.0%	1.9%	0.828
Hx HTN (%)	58.3%	63.5%	0.012
Smoker (%)	20.2%	20.9%	0.687
Hx prior pelvic radiotherapy (%)	8.0%	11.6%	0.002
Hx pelvic surgery (%)	47.2%	48.3%	0.624
Hx chemotherapy within 90 days (%)	39.0%	34.4%	0.026
Functional status: dependent/partially dependent (%)	1.3%	1.4%	0.772
Bowel prophylaxis strategy			
Mechanical bowel preparation (%)	22.2%	21.1%	0.813
Oral antibiotic bowel preparation (%)	6.2%	8.8%	0.038
Operative characteristics			
Surgical antibiotic prophylaxis longer than 24 h (%)	23.2%	25%	0.024
Surgical approach: Open/Open assist/Hybrid (%)	67.9%	77.8%	<0.001
Operation time (minutes)	326.21	332.08	<0.001
Drain placement (%)	96.3%	96.7%	0.620
Tumor characteristics			
T stage: T2	30.8%	27.5%	
T stage: T3	40.9%	40.6%	0.384
T stage: T4	11.5%	13.8%	
Length of stay, in days (Mean)	6.21	9.00	<0.001
C. difficile occurrences	1.2%	2.5%	0.01

Note. POI: Postoperative ileus; BMI: Body mass index; ASA: American Society of Anesthesiologists; COPD: Chronic obstructive pulmonary disease; CHF: Congestive heart failure; HTN: Hypertension; Hx: History of; T: TNM Tumor "T" Stage.

POI is associated with increased morbidity, prolonged hospitalization, and elevated healthcare costs. For instance, in a retrospective analysis of 17,876 colectomy patients in the United States, Iyer et al. estimated an additional mean cost of $9000 per patient attributable to POI.[25]

Although the chi-square test indicated a statistically significant association between chemotherapy and reduced incidence of POI (34.4% vs. 39%, $p = 0.026$), the inverse of this relationship was noted in the univariate logistic regression models (OR 1.22, 95% CI 1.02–1.45, $p = 0.031$). This apparent discrepancy reflects the differing analytical frameworks: the chi-square test provides a bivariate comparison without adjustment for confounders, while logistic regression—despite being univariate in this case—models the log-odds of the outcome and can yield different significance levels due to its nonlinear nature. The attenuation of the association in the multivariate model further suggests confounding by other covariates such as age, comorbidities, or disease stage.

Enhanced Recovery After Surgery (ERAS) protocols have been developed to improve perioperative outcomes by promoting early recovery and reducing complications such as POI. Among the various

TABLE 3. **Univariate and multivariate logistic regression for factors associated with POI after radical cystectomy**

Parameter	Univariate	*p*-value	Multivariate	*p*-value
Age > 65	1.386 (1.049–1.830)	0.022	1.361 (1.029–1.800)	0.031
Smoking	1.034 (0.785–1.362)	0.810	1.052 (0.798–1.387)	0.718
Chemotherapy within 90 days	1.220 (1.025–1.452)	0.026	1.178 (0.941–1.476)	0.153
Prior pelvic RT	1.515 (1.161–1.978)	0.002	1.026 (0.828–1.271)	0.815
Prior pelvic operations	1.023 (0.866–1.209)	0.791	1.168 (0.817–1.670)	0.395
Dependent functional status	1.947 (0.595–6.638)	0.271	1.996 (0.609–6.539)	0.254
Diabetes	1.258 (0.939–1.684)	0.124	1.257 (0.939–1.684)	0.125
COPD	1.342 (0.889–2.026)	0.056	1.336 (0.885–2.019)	0.168
CHF	1.570 (0.470–5.242)	0.464	1.623 (0.483–5.449)	0.433
HTN	1.247 (0.995–1.564)	0.056	1.239 (0.987–1.553)	0.064
Open approach (as compared to minimal access approach)	1.542 (1.167–2.038)	0.002	1.273 (0.746–2.171)	0.376
Drain placement	1.124 (0.708–1.783)	0.621	1.015 (0.591–1.743)	0.957
ABP (as compared to no prophylaxis)	1.711 (1.155–2.536)	0.007	1.692 (1.140–2.511)	0.009
MBP (as compared to no prophylaxis)	0.871 (0.658–1.152)	0.333	1.149 (0.868–1.521)	0.330
SAP use for more than 24 h	1.378 (1.012–1.877)	0.042	1.460 (1.280–2.176)	0.040

Note. RT: Radiotherapy; COPD: Chronic obstructive pulmonary disease; CHF: Congestive heart failure; HTN: Hypertension; ABP: Oral antibiotic bowel preparation; MBP: Mechanical bowel preparation; SAP: Surgical antibiotic prophylaxis.

ERAS recommendations, the avoidance of mechanical bowel preparation (MBP) and oral ABP has been emphasized to mitigate the risk of ileus.[14,26] Despite the demonstrated benefits of ERAS pathways, POI continues to be a prevalent issue, likely due to inconsistent adherence to these guidelines. In our cohort, MBP was administered to 22% of patients, highlighting a notable deviation from ERAS recommendations.

Nationwide, substantial variability exists in the implementation of antibiotic prophylaxis protocols, including inconsistencies in antibiotic selection, timing of administration, intraoperative redosing, and duration of therapy. Among these, the duration of SAP represents one of the most frequent yet underreported deviations.[17,27–29] In our study, 23.4% of patients received SAP for more than 24 h postoperatively, contrary to American Urological Association (AUA) guidelines, which recommend a single preoperative dose. It is likely that the true rate of noncompliance is even higher, as the ACS NSQIP dataset does not capture detailed antibiotic dosing information, whether patient received a single dose or multiple doses within a 24-h period. The pathophysiological mechanism by which prolonged antibiotic exposure may contribute to POI is hypothesized to involve disruption of the gut microbiota, particularly when antibiotics are administered outside the prophylaxis window.[30]

This study has several notable strengths. It represents one of the largest retrospective analyses of RC patients to date, encompassing over 5000 cases. The robustness of our multivariate regression analysis enhances the reliability of our findings. To our knowledge, this is the first study to specifically investigate the impact of prolonged and potentially unnecessary SAP on bowel function and postoperative morbidity following RC.

Nonetheless, several limitations must be acknowledged. The retrospective design inherently introduces certain bias. Although we observed significant results on logistic regression analysis, it is important to note that this is an association rather than implied causality. Additionally, the dataset lacks granularity regarding the exact duration, antibiotic class, dosing, timing, or redosing of antibiotic prophylaxis, limiting our ability to fully assess compliance with AUA guidelines. Data on the type of urinary diversion (e.g., neobladder vs. ileal conduit) were not available, which may influence the risk of POI and confound the observed associations. Only a small proportion of patients received oral antibiotic bowel preparation (6.5%) which raises concerns about selection bias. ERAS adherence and pain management protocols cannot be assessed in ACS NSQIP database and implementation of such protocols may influence outcomes of

POI. Furthermore, in the absence of direct case-by-case review, the rationale for administering mechanical or antibiotic bowel preparation—including indications related to usage of large bowel—could not be ascertained.

In conclusion, this study provides important insights into the consequences of deviations from antibiotic stewardship practices in the context of RC. Our findings underscore the need for greater adherence to evidence-based perioperative protocols, particularly regarding the use of ABP and SAP, to improve bowel recovery and reduce postoperative morbidity. Coordinated efforts at institutional, national, and international levels are warranted to standardize care, enhance compliance with guidelines, and ultimately improve patient outcomes. Future research should focus on randomized clinical trials on the utility of SAP and ABP in RC, and associated bowel recovery outcomes.

Conclusions

This large, retrospective analysis identifies oral antibiotic bowel preparation and prolonged surgical antibiotic prophylaxis as independent factors associated with postoperative ileus (POI) following radical cystectomy. Despite established guidelines from ERAS and the AUA, deviations in perioperative antibiotic practices remain prevalent and may contribute to increased postoperative morbidity and healthcare utilization. These findings underscore the critical need for improved adherence to evidence-based perioperative protocols and enhanced antibiotic stewardship to optimize outcomes of urologic oncology surgery.

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Author Contributions

Study conception and design: Sri Saran Manivasagam, Joseph Y. Clark, Jay D. Raman; Data collection: Sri Saran Manivasagam, Joseph Y. Clark, Jay D. Raman; Analysis and interpretation of results: Sri Saran Manivasagam, Joseph Y. Clark, Jay D. Raman; Draft manuscript preparation: Sri Saran Manivasagam. All authors reviewed and approved the final version of the manuscript.

Availability of Data and Materials

The ACS NSQIP is available to all participating institutions and cannot be shared due to regulatory requirements.

Ethical Approval

The study was deemed exempt from institutional ethics approval due to the use of de-identified data.

Conflicts of Interest

The authors declare no conflicts of interest.

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