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ORIGINAL ARTICLE

Predictors of surgical site infection after radical cystectomy: should we enhance surgical antibiotic prophylaxis?

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Abstract

Purpose To compare surgical site infections (SSI) rate after radical cystectomy (RC) over time and ascertain whether antibiotic prophylaxis should be enhanced.

Methods All medical records of RC patients in a single tertiary uro-oncology center between 2007 and 2017 were analyzed. SSI was defined using the criteria of the US Centers for Disease Control and Prevention. All bacterial culture results and antimicrobial resistance rates were recorded. Lastly, multivariable logistic regression analysis was performed to ascertain SSI predictors.

Results RC was performed in 405 patients, of which 96 (23.7%) developed SSI. No differences were demonstrated in the mean age, gender, NIDDM prevalence, neoadjuvant chemotherapy, positive preoperative urine culture, bowel preparation, and surgery time between both groups. However, statistically significant higher median BMI, age-adjusted Charlson Comorbidity score, usage of ceftriaxone preoperatively, and intensive care unit (ICU) hospitalization were noted in SSI patients. Overall, 62/96 (63.5%) SSI patients had a positive wound culture, with only 16.7% of the pathogens being sensitive to their perioperative antibiotics. Lastly, on multivariable analysis rising BMI, preoperative ceftriaxone and ICU hospitalization were associated with a higher SSI rate.

Conclusions Preoperative BMI reduction, and maximal preoperative medical optimization in an attempt to lower ICU admittance rates, should be part of the ideal strategy for lowering SSI rates. Additionally, preoperative antibiotics should be enhanced to harbor-wide spectrum coverage, based on local resistance rates.

Keywords Radical cystectomy · Surgical site infection · Surgical antibiotic prophylaxis

Abbreviations

AUA	American Urology association
BMI	Body mass index
CDC	US Centers for Disease Control and Prevention
EAU	European association of Urology
ERAS	Enhanced recovery after surgery
IC	Ileal conduit
ICU	Intensive care unit
NC	Neoadjuvant chemotherapy
OR	Odds Ratio
RC	Radical cystectomy
RR	Relative risk
SAP	Surgical antibiotic prophylaxis
SSI	Surgical site infection

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Introduction

Radical cystectomy (RC) with urinary diversion is the primary treatment for muscle-invasive bladder cancer. Surgical site infections (SSIs), which reportedly amount to a fifth of all healthcare-associated infections [1], are a common cause of postoperative morbidity [2]. SSI can cause pain, delayed wound healing, delay of adjuvant chemotherapy, time lost from work and, rarely, death [3]. Furthermore, SSIs contribute to increased costs owing to more extended hospital stays, and readmissions. The resulting use of additional antibiotics ultimately leads to the development of resistant strains. Past studies demonstrate that patients with SSI are 60% more likely to be admitted to the intensive care unit (ICU), five times more likely to be readmitted, and twice as likely to die [4].

The rate of SSI after RC ranges between 2.9 and 45% [5, 6] in different series. This variation is possibly related to differences in patient population or comorbidities, surgeon or center experience, perioperative care, or discrepancies in SSI definition and report [7]. Aside from patient-related factors affecting SSI, such as smoking, obesity, and diabetes, there are also procedure-related factors, such as blood transfusion and surgery duration [8]. Several methods have been offered to reduce the incidence of SSI, namely mechanical and antimicrobial bowel preparation, implementation of surgical antibiotic prophylaxis (SAP) [9, 10], and changing the skin preparation [11]. Immuno-nutrition, entailing perioperative enteral feeding with specialized immune-nutrition drinks, has also recently been shown to reduce infections. [12].

In recent years, the enhanced recovery after surgery (ERAS) consensus panel was established to implement evidence-based perioperative treatment protocols intended to attenuate the stress response to surgery, thus reducing hospital stay lengths, and complications including infections such as SSI [13]. In 2013, an ERAS protocol was introduced for RC patients, most of which deduced from previous guidelines on colorectal and pelvic surgery [14]. The ERAS protocol recommends administrating a single dose of antimicrobial agent less than 1 h before skin incision, with adequate antimicrobial coverage (the ideal agent combination yet to be established). [14].

According to the EAU guidelines [15] and by the recommendation of our institutional infectious disease specialists, our center began gradually modifying our traditional preoperative RC pathway in 2014, in a stepwise approach, with initially abandoning bowel preparation, and then supplanting intravenous ampicillin, gentamycin, and metronidazole with a single dose of intravenous ceftriaxone and metronidazole. In this context, we endeavored to analyze the SSI rate, ascertain the resistance rates of bacteria isolated from wound cultures, and analyze SSI risk factors. We hypothesized that the gradual implementation of some of the changes included in the ERAS protocol would result in a reduction of SSI rate, without the need to enhance the recommended SAP.

Methods

Definition of surgical site infection

SSI was defined according to the US Center for Disease Control and Prevention (CDC) [16] as infection of the skin or subcutaneous tissue (superficial SSI), or infection of the deep soft tissue of the incision (deep SSI), or infection of any part of the anatomy other than the incision (organ/space SSI), occurring within 30 days after the operation. In all three of these SSI subtypes, at least one of the following has to occur:

(1) Purulent drainage with or without laboratory confirmation.
(2) Pathogenic organisms isolated from an aseptically collected culture;
(3) For superficial SSI—Inflammatory symptoms at the incision site (pain, tenderness, localized swelling, redness, or heat); or incision opened by surgeon, unless culture-negative. For deep SSI and organ/space SSI—an abscess/infection is found on direct examination.
4) The surgeon or attending physician must make the diagnosis.

Patient cohort and data collection

After receiving approval by the institutional ethics committee, we retrospectively analyzed the medical records of all patients who underwent RC and urinary diversion for muscle-invasive bladder cancer or high-risk non-muscle-invasive disease, at a single tertiary uro-oncology center between 2007 and 2017. All patients underwent open RC by one of three surgeons (JB, OY, and DK), using the same midline incision and technique. All three surgeons were trained in the same center and were taught by the same physician (JB). All neobladders and ileal conduits were created using the ileum segment. Data collected included age, gender, age-adjusted Charlson Comorbidity Score, including whether the patient had diabetes, body mass index (BMI), neoadjuvant chemotherapeutic (NC) treatment, preoperative urine culture results, type of bowel preparation, SAP, operative and hospitalization time, urinary diversion (ileal conduit [IC], or orthotopic bladder reconstruction), intensive care unit (ICU) admission, postoperative complications according to the Clavien-Dindo classification, type of SSI that had developed within 30 days of the procedure, and if it necessitated surgical intervention. Lastly, all positive bacterial culture results and antimicrobial resistance rates were recorded.

Perioperative management and wound monitoring

Supplemental Table 1 depicts the perioperative management protocols used for all patients before and after implementation of the ERAS guidelines in 2014 in our center. However, the implementation of ERAS in our center was gradual, and only some of its components were adopted initially. These mainly included abandoning of bowel preparation, and changing the preoperative prophylactic antibiotics from ampicillin, gentamycin, and metronidazole to ceftriaxone and metronidazole, due to its broad-spectrum coverage against gram-positive, Gram-negative bacteria and anaerobic bacteria. If patients were allergic to penicillin, either clindamycin or vancomycin was used. Later on, preoperative nutritional support, given by a certified hospital-based dietician was performed. Additionally, if encountered, anemia was corrected preoperatively, and smoking cessation was encouraged. Preoperatively, sterile urine was confirmed in all patients, with or without the need for a short course of oral antibiotics as determined by recent urine culture findings, both pre-and post-ERAS implementation.

Postoperatively, pre-ERAS patients were treated with intravenous cefuroxime antibiotics. These were administered until oral intake was established. At this stage, patients were given oral antibiotics in the form of cefuroxime or ofloxacin until discharge. A single dose of intravenous ceftriaxone was also given before stents removal. In the post-ERAS period, postoperative antibiotics were abandoned, except for the single dose of ceftriaxone administered before stents removal. Postoperatively, in both pre-ERAS and post-ERAS periods, patients were monitored, and their surgical wounds were assessed at least twice daily. Wounds were examined for erythema or discharge. When SSI was suspected, the overlying skin staples were partially removed, and fluid discharge drained and sent for bacterial culture and sensitivity assays. In the presence of systemic infection, empirical treatment with broad-spectrum intravenous antibiotics was initiated and directed subsequently based on culture susceptibility and consultation with an infectious diseases specialist. Any wound meeting the CDC criteria for infection was defined as either superficial, deep or space/organ SSI [16]. Surgical intervention was explicitly decided for each case, based on the clinical status of the patient and the severity of the SSI.

Statistical analysis

Descriptive analyses (median with range) were used for continuous variables, proportions for discrete variables, and comparative tests included Chi-square for discrete variables and Mann–Whitney *U* test for continuous variables. Multivariable logistic regression analysis was performed to identify factors predicting SSI. A priori covariates in the model included age, gender, BMI, the presence of diabetes, preoperative antibiotics, preoperative bowel preparation, surgery duration, and ICU admittance. All the factors initially changed by ERAS were incorporated in the model. The goodness of fit was assessed using the Lemeshow and Hosmer method [17]. Statistical tests were two-tailed, and a p value of < 0.05 was considered statistically significant. All analyses were conducted using SPSS software version 23.0 (SPSS Inc., Chicago, IL, USA).

Results

The cohort included 405 consecutive patients, and 96 (23.7%) were diagnosed with SSI. Table 1 compares the preoperative clinical data of patients with and without SSI. No differences were demonstrated between the groups in age, gender, diabetes, pathology, receipt of NC, the rate of preoperative positive urine culture, and bowel preparation. However, patients with SSI had a higher median BMI and age-adjusted Charlson score. Additionally, they were more likely to be given preoperative ceftriaxone + metronidazole.

Table 2 demonstrates operative and postoperative differences among patients developing and not developing SSI. Significant differences between the two groups were noted with SSI patients having a significantly higher rate of ileal conduit (83.3% vs. 66.7%, $p = 0.002$). A total of 80.2% of all SSI were superficial, while only one patient required negative pressure wound therapy (VAC). SSI patients had endured a higher rate of complications and were more likely to be admitted to the ICU (13.7% vs. 4.5%, $p = 0.002$). A total of three patients (3.1%), all of whom had an SSI, had a postoperative course complicated by bowel leak. Additionally, six patients had a urine leak, with four of them diagnosed with an SSI (4.2%), while the other two did not have an SSI (0.6%). In all six patients, the median hospitalization time was approximately 30 days with their bilateral stents left until they were discharged. All six patients had an abdominal drain inserted, and 4/6 (66.7%) also required a temporary nephrostomy tube. Importantly, 16 patients (16.7%) who had an SSI required surgical intervention, compared to none of the patients who did not have an SSI. Lastly, two patients (2.1%) from the SSI group and one patient (0.3%) who did not have an SSI died during the immediate postoperative period.

Of the SSI patients, 61 (63.5%) had a positive postoperative wound culture. In only 10/63 (15.9%) of these patients, the isolated pathogen was sensitive to the combination of antibiotics administered preoperatively (6% in patients given ceftriaxone, and 24% in patients given ampicillin + gentamycin). Figure 1 illustrates the distribution of pathogens, the most common being coagulase-negative *Staphylococci*, followed by Klebsiella and *E coli*. Supplemental Fig. 1 depicts the antibiotic resistance rates to each antibiotic of all isolated SSI pathogens. A meager resistance rate was noted for vancomycin, ertapenem, amikacin, imipenem, and meropenem. Significantly high resistance rate was recorded with ampicillin (85%), ceftriaxone (70.6%), and gentamycin (59.3%).

On multivariable logistic regression analysis evaluating predictors of SSI, rising BMI, SAP including ceftriaxone + metronidazole vs. Ampicillin + gentamycin + metronidazole and, postoperative ICU admittance were associated with the higher risk of SSI (Table 3).

Table 1 Patient preoperative clinical characteristics

	Surgical site infection	No surgical site infection	*p* value
Number of patients, *n* (%)	96 (23.7%)	309 (76.3%)	–
Median age (range)	68 (34–87)	67 (18–89)	0.477
Sex, *n* (%)			0.2
Male	74 (77.1%)	256 (82.8%)	
Female	22 (22.9%)	53 (17.2%)	
Median BMI (range)	28.1 (18.1–41.6)	25.6 (18.5–46.8)	< 0.001
Diabetes, *n*(%)	31 (32.3%)	87 (28.2%)	0.436
Median age-adjusted Charlson score (range)	5.17 (1–9)	4.67 (1–10)	0.008
Pathology warranting radical cystectomy, *n*	92	302	0.12
TCC	3	1	
Squamous cell carcinoma	0	2	
Sarcoma	1	2	
Small cell carcinoma	0	1	
Adenocarcinoma	0	1	
Prostate			
Rhabdomyosarcoma			
Received neoadjuvant chemotherapy, *n* (%)	18 (18.8%)	79 (25.6%)	0.172
Preoperative positive urine culture, *n* (%)	20 (22.5%)	55 (18.7%)	0.718
Bowel preparation before surgery, n (%)	55 (57.3%)	208 (67.3%)	0.072
Preoperative intravenous antibiotics, *n* (%)	60 (62.5%)	234 (76.2%)	0.008
Ampicillin + gentamycin + metronidazole	36 (37.5%)	73 (23.8%)	
Ceftriaxone + Metronidazole			

BMI body mass index

Table 2 Operative and postoperative clinical characteristics

	Surgical site infection	No surgical site infection	*p* value
Median surgery time, min (range)	288 (159–471)	285 (114–501)	0.51
Median Hospitalization time, days (range)	12 (9–58)	12 (7–66)	0.5
Type of diversion, *n* (%)			
Ileal conduit	80 (83.3%)	206 (66.7%)	0.002
Neobladder	16 (16.7%)	103 (33.3%)	
ICU hospitalization, *n* (%)	13 (13.7%)	14 (4.5%)	0.002
Complications (Clavien-Dindo), n (%)	0	134 (43.4%)	< 0.001
None	0	129 (41.7%)	
Grade 1	76 (79.1%)	39 (12.6%)	
Grade 2	3 (3.1%)	4 (1.3%)	
Grade 3a	12 (12.5%)	1 (0.3%)	
Grade 3b	1 (1%)	1 (0.3%)	
Grade 4a	2 (2.1%)	0	
Grade 4b	2 (2.1%)	1 (0.3%)	
Grade 5			
Type of SSI			
Superficial	77 (80.2%)	–	
Deep	15 (15.6%)		
Organ/space	3 (4.2%)		
SSI required exploration	16 (16.7%)	–	–

ICU intensive care unit, *SSI* surgical site infection

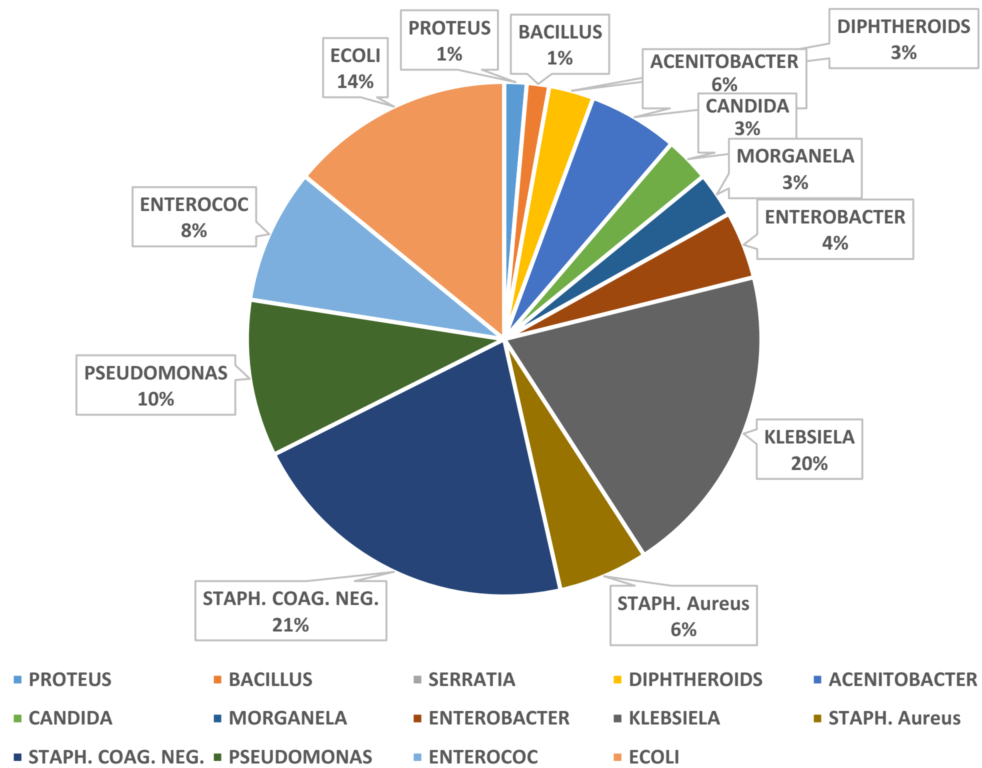

Fig. 1 - Distribution of pathogens from positive wound cultures

Comment

Similar to prior reports, our study found an SSI rate of 23.7% with a high resistance rate of cultured pathogens to prescribed preoperative antibiotics, for both regimens used. Our study also demonstrated that patients developing SSI were more likely to have a higher BMI, be given preoperative ceftriaxone, and postoperatively admitted to the ICU. A possible explanation for the high incidence of SSI in our center is the proportion of obese and morbid patients, demonstrating a higher ICU admittance rate. Higher BMI is a known contributor to increased SSI risk [18], and ICU admittance is intuitively recognized as a risk factor. Our results also demonstrate that ceftriaxone is not sufficient in preventing SSI development, showing that only 6% of the pathogens grown from wound cultures were susceptible to it.

The rate of documented SSI after RC differs between existing studies and ranges between 2.9 and 45%. [5, 6, 9, 10, 19] This vast range stems from various reasons, including how SSI was defined. Only one previous study defined SSI among RC patients using the strict CDC guideline definition, depicting an even higher SSI rate of 33% [20].

The CDC has just recently published its long-awaited update of the 1999 guidelines for prevention of SSI [21]. Unfortunately, due to lack of appropriate evidence, the authors make no definitive recommendation on many pertinent issues. Key topics include the use of SAP to achieve adequate bactericidal concentrations in serum and tissues,

Table 3 Multivariable logistic regression model evaluating risk factors for SSI development

	Odds ratio	95% CI	*p* value
Age	1.015	0.988–1.043	0.285
Gender (male reference)	1.8	0.965–3.386	0.064
BMI	1.079	1.015–1.146	0.014
Diabetes	0.834	0.466–1.491	0.54
Preoperative bowel preparation (no bowel preparation—reference)	1.2	0.6–2.419	0.586
Preoperative antibiotics (ceftriaxone + metroniazole vs. ampicillin + gentamycin + metronidazole)	2.047	1.021–4.104	0.044
Surgery duration	1.001	0.998–1.005	0.463
ICU hospitalization after surgery (before SSI developed)	3.637	1.295–10.214	0.014

BMI body mass index, *ICU* intensive care unit, *SSI* surgical site infection glycemic control with a glucose target < 200 mg/dL, maintenance of normothermia, and a higher fraction of inspired oxygen used in patients with normal pulmonary function during surgery and after extubation [21]. Despite guideline recommendations, adherence rates by urologic surgeons worldwide are often suboptimal. A recently published population-based study from the US demonstrated that only 15% of patients received guideline-based SAP [9].

In colorectal surgery, the use of multimodal ERAS regimens have reduced postoperative morbidity and length of stay [22]. Since a high number of ERAS components are generic to abdominal surgery, they have been implemented in RC patients without confirmatory evidence [23]. A recent meta-analysis assessing the impact of ERAS on patients undergoing abdominal and pelvic surgeries demonstrated a reduction in SSI with a relative risk (RR) of 0.75, (CI 95% 0.58–0.98, $p = 0.004$) [24]. Despite this, general and colorectal surgeries do not necessarily apply to RC, given that the urinary tract is no longer isolated from the gastrointestinal tract [9]. Therefore, there is a lack of data regarding proper antibiotic prophylaxis, and data from randomized trials are required for patients undergoing RC.

Positive wound cultures were found in more than 60% of the patients manifesting SSI with only ~ 15% of the isolated pathogens being sensitive to the pre-administered preoperative antibiotic. Of the three most common pathogens, two were Gram-negative, and the third was coagulase-negative *Staphylococci*, a Gram-positive bacteria. Coagulase-negative *Staphylococci* are a major nosocomial pathogen, having a substantial impact on human life and health [25]. A large population-based study demonstrated that prophylactic antibiotics effective against skin, genitourinary, and enteric flora, given for less than 24 h, had the best outcomes [9]. The key is to cover both Gram-positive and Gram-negative bacteria and, therefore, a combination of broad-spectrum antibiotics is probably the most appropriate SAP [9]. Furthermore, surgeons should strive to implement the infectious disease society of America recently published guidelines, endorsing the implementation of an antibiotic stewardship program. The stewardship mandates that patients receive targeted antibiotics for the shortest possible time to avoid development of resistance and adverse effects. [26] Adhering to the recommendations of the Infectious Disease Society of America together with the recent CDC guidelines [21] mentioned previously, and the similar WHO guidelines [27], should successfully lower SSI rates.

Some possible conditional recommendations can be suggested additionally, although their level of evidence is not high. These include but not limited to preoperative patient bathing, goal-directed fluid therapy, and preoperative administration of oral multiple nutrient enhanced formulas, especially in underweight patients [27]. On the other hand, recommendations proved to be unsuccessful in lowering SSI rates, and might even increase it, include administration of postoperative total parenteral nutrition [28], wound irrigation, advanced dressings instead of standard dressings, and continuation of postoperative SAP [27].

It is important to remember that the ideal SAP for RC and for any surgery for that matter may also vary in time and place due to changes in the bacterial flora and various resistance rates. General and local guidelines must frequently be updated, and diligent monitoring must be continued. Due to the results of this study, we are considering altering our usage of preoperative ceftriaxone + metronidazole, to a combination of antibiotics with a more broad spectrum.

Our study has several limitations. These include the retrospective nature of it and the fact that this is a single-center experience, although a tertiary high-volume oncology referral center. Furthermore, even though all cases were done by three physicians trained in the same center, it would be reasonable to assume that some differences in the surgical technique had developed over the years, which could have affected the SSI rate and the rate of other complications. Additionally, the study spans a period of gradual ERAS implementation, incorporating only some of the ERAS factors, and where most of the patients were still undergoing through the "older" pathway. Additional limitations include lack of data on smoking history and perioperative blood transfusions, which have been demonstrated to be an SSI risk factor in RC [8]. Another limitation is the inherent selection bias of patients undergoing surgery, especially in more recent years. This is due to several reasons, but especially due to the local two-tier healthcare system causing a clear selection bias. This results in the more diseased, obese, and morbid patients being operated in the public healthcare system, while the "healthier," and more fit patients, with a better socioeconomic status turning to the private health care system. Lastly, it is known that the antibiograms for infections differ by region and institution, and most likely will not be consistent with other institutions worldwide.

Conclusions

Adherence to proven guideline recommendations is crucial when attempting to decrease SSI rates. The ideal strategy should include preoperative BMI reduction, and maximal preoperative medical optimization to lower postoperative ICU admittance rates. Lastly, SAP must be enhanced to include a combination of broad-spectrum antibiotics with low resistance rates among local and institutional pathogens.

Author contributions HG: project development, data collection, data analysis, manuscript writing. CS: project development, data collection, data analysis, manuscript writing. HT: data collection, data analysis. RM: data collection, data analysis, manuscript editing. JB: project development, manuscript editing. DM: project development, manuscript editing. DK: project development, manuscript editing. OY: project development, data analysis, manuscript writing and editing

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Research involving human participants and/or animals As this was a retrospective study, this study did not contain any contact with human participants or animals performed by any of the authors.

Informed consent As this was a retrospective study, no informed consent was required for this study by the internal review board.

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