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Urologic Oncology: Seminars and Original Investigations 34 (2016) 121.e9–121.e14

UROLOGIC ONCOLOGY

Original article

The effect of broader, directed antimicrobial prophylaxis including fungal coverage on perioperative infectious complications after radical cystectomy

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Received 4 June 2015; received in revised form 28 August 2015; accepted 9 October 2015

Abstract

Objectives: Radical cystectomy (RC) with urinary diversion has a significant risk of infection. In an effort to decrease the rate of infectious complications, we instituted a broader, culture-based preoperative antimicrobial regimen, including fungal coverage, and studied its effect on infectious complications after RC.

Materials and methods: In May 2013, antimicrobial prophylaxis for RC was changed at our institution after review of previous positive cultures. Ampicillin-sulbactam 3 g, gentamicin 4 mg/kg, and fluconazole 400 mg replaced cefoxitin. Patients undergoing RC from May 2011 to May 2014 were included. Before and after implementation of the new regimen, 30-day infectious complications (positive blood culture, urinary tract infection, wound infection, abscess, and pneumonia) and adverse events (*Clostridium difficile*, readmission, and mortality) were compared. Multivariate logistic regression was used to identify independent risk factors for infection while controlling for covariates.

Results: In total, 386 patients were studied (258 before the change and 128 after). The overall infection rate decreased with the new regimen (41% vs. 30%, $P = 0.043$) with improvements in wound (14% vs. 6%, $P = 0.025$) and fungal (10% vs. 3%, $P = 0.021$) infections. Median length of stay decreased from 8 (interquartile range [IQR]: 7–12) to 7 (IQR: 7–10) days ($P = 0.008$). On multivariate analysis, the new regimen decreased the risk of infections (odds ratio [OR] = 0.58, 95% CI [0.35–0.99], $P = 0.044$) whereas body mass index, operating room time, smoking, and total parenteral nutrition increased the risk (all $P < 0.05$).

Conclusions: Risk factors for infection after RC include body mass index, operating room time, smoking, and total parenteral nutrition use. Changing from cefoxitin to broader, culture-directed antimicrobial prophylaxis, based on institutional data to include antifungal coverage, decreased postoperative infections.

Keywords: Antibiotic Prophylaxis; Antibacterial Agents; Antifungal Agents; Cystectomy; Infection

1. Introduction

Radical cystectomy (RC) with urinary diversion is the gold standard for muscle-invasive bladder cancer but is associated with considerable perioperative morbidity. Specifically, there is significant risk of infectious complications, estimated at 25% to 44% [1–5]. Although certain aspects of preoperative management, such as bowel preparation [6,7], have been studied in attempts to improve perioperative outcomes, there is a dearth of literature on the topic of antimicrobial prophylaxis for RC.

Guidelines for antimicrobial prophylaxis, such as the American Urological Association Best Practice Statement [8], are hampered by a lack of RC-specific research and generally based on colorectal surgery literature. However, relevant bacteria may differ given the obligatory transection of the urinary system during RC as well as variability in the

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http://dx.doi.org/10.1016/j.urolonc.2015.10.007
1078-1439/

segment of bowel used. Fungal infections may also be more common in RC as approximately 9% of postoperative urinary tract infections are caused by Candida [1].

Given that infectious complications are debilitating and may include multiple types of organisms including gut-derived bacteria, urinary organisms, and skin flora, a more aggressive perioperative antimicrobial regimen may be needed to decrease the unacceptably high rate of infectious complications after RC. Therefore, we examined the causative pathogens for perioperative infections after RC over a 2-year period and broadened our antimicrobial prophylaxis in a directed fashion. We then implemented the new regimen at our institution in May 2013. *Our primary objective was to compare the rate of perioperative infectious complications after RC before and after the implementation of a new regimen for antimicrobial prophylaxis*.

2. Materials and methods

In May 2013, a multidisciplinary review of positive cultures from postoperative RC patients at our institution was performed, examining the 2 prior years. Outcomes and culture data were limited to 30 days after surgery. *Preoperative cultures were performed at surgeon discretion based on clinical history*. Patients were cultured postoperatively if there was clinical suspicion of infection, and analysis included any positive blood, urine, abscess, sputum, or wound culture results. The standard preoperative antimicrobial prophylaxis before the change was cefoxitin 2 g IV, which was lowered to 1 g if the patient weighed less than 60 kg. The alternative regimen for penicillin-allergic patients was a fluoroquinolone. Antibiotics were given for 24 hours.

After review, a broader antimicrobial regimen directed toward the common organisms was instituted: ampicillin-sulbactam 3 g IV, gentamicin 4 mg/kg IV, and fluconazole 400 mg PO/IV. Ampicillin-sulbactam was redosed every 6 hours and continued postoperatively for 24 hours, whereas gentamicin and fluconazole were given as single-time doses *considered to provide 24 hours of coverage*. Fluconazole was taken orally before arriving in the hospital for maximum absorption and to minimize cardiac side effects. In rare circumstances where a patient did not take fluconazole orally, it was given intravenously. *Intravenous medications were given within 60 minutes of incision before and after the change*. For patients who were allergic to penicillin, the regimen was vancomycin 15 mg/kg (maximum 2 g), gentamicin 4 mg/kg IV, metronidazole 500 mg IV, and fluconazole 400 mg PO/IV. The choice of antibiotics, dosing, and route was chosen after multidisciplinary review by urologists, infectious disease specialists, and pharmacists.

All patients who underwent RC at our institution after the change on May 23, 2013, were given the new regimen. After 1 year, patients given the new regimen (May 23, 2013−May 31, 2014) were compared to historical controls (May 1, 2011−May 22, 2013). We used an IRB-approved, institutional cystectomy database for all clinical information. Patients were excluded if they had a known infection immediately before surgery ($n = 6$), did not have a bladder or urethral malignancy ($n = 6$), or did not undergo a urinary diversion ($n = 3$). Data reviewed included age, sex, race, body mass index (BMI), age-adjusted Charlson Comorbidity Index (CCI), smoking status, neoadjuvant chemotherapy, prior radiation, BCG history, diversion type, pathologic stage, robotic approach, operating room time (OR Time), and use of total parenteral nutrition (TPN). Smoking status was considered positive if patients were current or former habitual smokers. Open vs. robotic approach was determined by surgeon and patient preference, and bowel preparation was used only for colonic diversions. Alvimopan was used in all patients and discontinued after the patient had a bowel movement. Diet was advanced with return of flatus, and TPN was generally reserved for patients unable to tolerate oral intake after 7 days.

Outcomes of 30-day infectious complications included positive blood or sputum culture results, urinary tract infection, abscess, fungal infection, wound infection, and pneumonia. Cultures included those taken at outside institutions, during inpatient admission, and outpatient clinics. The primary outcome was overall infection rate. Of note, if a patient's culture grew multiple different organisms, each organism was accounted for in the categories of individual species, but only a single infection was included in the primary outcome of overall infection rate.

Adverse events were analyzed, including *Clostridium difficile* infection, readmission, and mortality for 30 days after RC. Medians of continuous variables were compared using Mann-Whitney U test and categorical variables using a chi-squared test. Multivariate logistic regression was used to identify independent risk factors for infectious complications while controlling for covariates. All tests were 2 tailed, and a threshold of $P < 0.05$ was considered significant for statistical analyses.

3. Results

Baseline characteristics of the study population, which included 258 patients before and 128 after the antibiotic change, are shown in Table 1. Before the change, patients had a lower median CCI (3 [interquartile range {IQR}: 2–4] vs. 4 [IQR: 3–5], $P < 0.001$) and a higher rate of neoadjuvant chemotherapy (18% vs. 9%, $P = 0.029$). Overall, penicillin allergy was reported in 54/386 (14%) patients, which was similar between groups ($P = 0.365$). All other demographic and clinical factors were similar between cohorts ($P > 0.1$).

The postoperative outcomes for the cohorts are shown in Table 2. An infectious complication occurred in 106/258 patients (41%) before the antibiotic change compared with