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REVIEW ARTICLE

Impact of antibiotic prophylaxis in post-radical cystectomy complications: Should it be enhanced? A systematic review article.

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ABSTRACT… Objective: To evaluate the efficacy and outcome of antibiotic prophylaxis (AP) in patients undergoing radical cystectomy. **Study Design:** Retrospective Review. **Setting:** Armed Forces Institute of Urology, Rawalpindi. **Period:** January 2020 to January 2021. **Methods:** On patients with bladder cancer undergoing radical cystectomy. Studies were selected irrespective of gender, published in English language in the last five years. PubMed data base is used to review articles. **Results:** This article attempted to formulate a seat of guidelines through reviews published in various journals regarding AP for post-radical cystectomy patients. Antibiotic prophylaxis is highly recommended for RC since infectious complications accounts for a major complication in postoperative period. The strategy of implementing AP in RC patients could result in the most favorable patient reported outcomes. **Conclusion:** Our review supports the policy of AP in all patients with bladder cancer undergoing radical cystectomy. Postoperative infections are the modifiable risk factors which can be prevented by antibiotic prophylaxis. Continued efforts are needed to establish an optimal preoperative management plan.

Key words: Radical Cystectomy, Antibiotics Prophylaxis, Infections.

INTRODUCTION

The fourth most common urological cancer in the United States, bladder cancer is linked to smoking and is caused by long-term exposure to known carcinogens. The incidence of bladder cancer is approximately four times higher in men than in women, and an estimated 80,470 new cases are anticipated in the US in 2019.[1] Bladder cancer incidence rose by almost 50% between 1950 and 2005, however it decreased by 1% year between 2006 and 2015. During the same time period, the mortality rate from bladder cancer decreased by about 33%.[2]

The primary treatment for bladder cancer that is localized is radical cystectomy (RC). Because it is a lengthy, exceedingly morbid process that includes surgery on the digestive, urinary, and lymphatic systems, complications are common following such a difficult procedure. Infection makes up 25% of all early complications after radical cystectomy.[3] Relatively little information is available about the use of antibiotic prophylaxis (AP) to avoid post-operative infections following RC. Patients may benefit from AP to reduce infectious problems after surgery, as post-operative infections are a modifiable pre-operative risk.

AP is being utilized to improve the quality of surgery due to the high prevalence of systemic and surgically sited infections. In order to lower the risk of both local and systemic post-procedural infections, AP involves the systemic infusion of an antimicrobial drug prior to the surgery. The overall RC mortality rate has dropped from 40% to less than 4% over the past few decades, and the perioperative mortality rate has dropped from 20% to less than 2%.[4] Serious complications still affect about 30% of patients during hospitalization and up to 60% of patients within 90 days after open and laparoscopic surgery,

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despite a progressively reduced incidence in complications.[4,5] Complications prolong the total length of stay (LOS) in a hospital, and significantly increase total treatment costs.[6]

Prophylactic antibiotics are often misused in various surgical operations, as has been claimed for more than two decades.[7] Surgical antimicrobial prophylaxis (SAP) is recommended only when the potential benefits outweigh the dangers. When prescribing AP, one should take into account the anticipated costs, adverse effects, and emergence of bacterial resistance. The prophylactic agent should be effective against the organism most likely to cause infection in the early and late post-operative periods.

The 2008 Best Practice Policy Statement on Urologic Surgery and Antimicrobial Prophylaxis of the American Urological Association (AUA) [8] recommends that antimicrobial prophylaxis be given for no more than 24 hours during the perioperative period. The only exception was a cystectomy, where antibiotics were administered for seven days following surgery and metronidazole, an anti-anaerobic parenteral drug, for five days. This prolonged antibiotic treatment resulted from the use of an ileal segment to divert urine following bladder removal.[9]

This article provides a literature review of what is currently known about the antimicrobial prophylaxis efficacy after RC. It identifies current gaps in the literature while suggesting that AP might prove useful in patients undergoing radical cystectomy.

METHODS

We searched the literature for a traditional review in order to ascertain the efficacy of antibiotic prophylaxis after radical cystectomy. The primary source of publications was the PubMed database.

Assessment for eligibility: We included human studies regardless of ethnicity, gender, or age. A wide range of study designs that had been published globally in English during the preceding ten years were included. Non-human was excluded from the analysis. The search terms were radical cystectomy, prophylaxis, and antibiotics.

Abstracts and full manuscripts resulting from this search were reviewed for clinical effectiveness of antibiotic prophylaxis after radical cystectomy. All the data was collected ethically and legally.

DISCUSSION

Using data available on PubMed, we have asses the role of prophylactic antibiotics after radical cystectomy. The total number of selected studies specific to antibiotic prophylaxis for radical cystectomy included in this article is 38 published all around the world in English language only. The total number of studies searched using key word radical cystectomy were 7209, full text studies were 2148, after applying inclusion and exclusion criteria we have 1637 studies in total. Using the keyword prophylactic antibiotics, we have 21099 studies in total out of which 4039 were full text studies and 1407 studies with inclusion /exclusion criteria. The total no of patients included in this review article is 980,974 irrespective of age, caste, color and gender. Since it's a traditional review article so quality assessment tool has not been used.

Several lines of evidence have suggested that AP play a major role in preventing post-operative infections after RC.

Clinical Characteristics and Biomarkers predictive of Benefit

Although urological laboratory tests and risk grouping are prognostic, a predictive molecular biomarker that can correlate with the impact of AP on postoperative infectious pathology is the ideal situation. Clinical factors such as pain and presence of elevated inflammatory markers may assist in making treatment decisions.

Risk of complications post-radical cystectomy?

A study published in ELSEVEIER shows the increased length of stay in hospital prior to surgery is directly related to increased risk of postoperative infections.[10] It emphasizes on same day admission policies to help minimize complications risk post-operatively. Another

study in Urol Oncol Journal shows the increased risk of surgically sited infections (SSI) in females undergoing RC.[11] However, this study is gender specific and lack patient factors and pathogenic microbes which are needed to prescribe the best measures for infection prophylaxis.

A study published by Matthew Mossanen in BJUI found that infections complications are among the costliest after RC within first 90 days[12] (Graph 1.1). A study by Medina-Polo J find out that radical cystectomy is associated with a high incidence of HAIs.[13] The study in BJUI focuses not only on the major complications but also minor as well along with their expected cost and the burden on the health care system while the latter one is associated with antibiotic pattern.

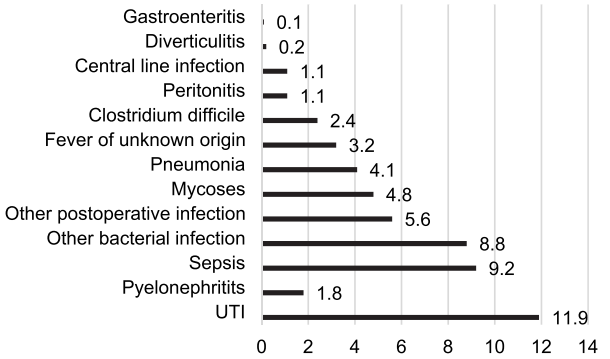

Figure-1. Infectious complication rates for patients undergoing RC

Study conducted at Mayo clinic shows the incidence of UTI post-radical cystectomy within 90 days.[14] This study explains the incidence of UTI but it's a single center study which lack other post-operative complications after RC. (Figure-2)

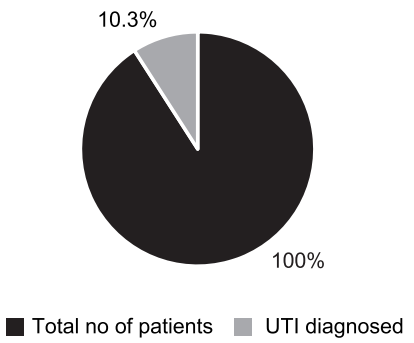

Figure-2. Incidence of UTI post-radical cystectomy; A study conducted at Mayo Clinic.

An article in Elsevier demonstrates that long duration of antimicrobial exposure is associated with clostridium difficile infection post-operatively.[15] A study in PubMed by Matthew Mossanen shows non-compliance rates of antibiotic by procedure.[16] Study in Elsevier emphasizes that perioperative antimicrobial prophylaxis guidelines should be followed while the latter one reveals that in certain situations there is significant evidence to continue AP beyond the immediate perioperative period. The standard of care for post-radical cystectomy over recent years has become better.

An article by Meera R. Chappidi evaluates the impact of blood storage duration with perioperative blood transfusion (PBT) on the risk of adverse post-operative outomes.[17] (Figure-3)

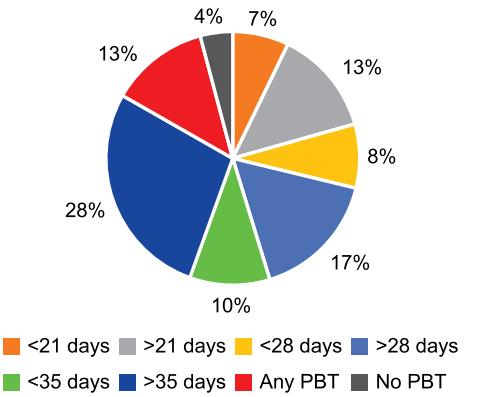

Figure-3. Morbidity stratified by average storage duration of RBC units transfused.

A study in Urol Oncol focuses on the importance of cofixitin vs culture-directed AP including antifungal coverage.[18] While another study compares the short and long term duration of AP in reducing post-operative complications. This article in Medicine (Baltimore) journal compares the short and long term prophylaxis, suggesting short term prophylaxis better in preventing infectious complications.[19] These studies showed the efficacy of AP which is a cornerstone of health care delivery post-radical cystectomy. The recent increased performance of broad spectrum antibiotic and widespread adoption of guidelines have led to the prevention of post-radical cystectomy complications. Therefore, we should adopt AP to decrease colonization with multi-drug resistant organisms.

A retrospective study with a small sample size in JKMC journal shows the incidence and causative pathogen involved in febrile urinary tract infection (FU). It shows enterococcus species to be the most common pathogen after RC while previous studies suggest escheria coli.[20] This study shows a positive strong association between FU as post-radical cystectomy complication. An article by Alden Prcic in Med Arch determine the most frequent early and late complications in different types of ileal urinary diversions. It shows the morbidity with ileal conduit in the first 30 days is 20-56%, and after 30 days is 28-81%.[21] Despite having a small sample size and age restricted to 40-80 years old this study provides support for previous studies showing that a match between post-operative complications and treatment protocol could result in more favorable outcomes.

Another article shows the financial loss and increased treatment costs caused by increased hospitalization time and deep surgical site infections (DSSI) after RC.[22] (Figure-4)

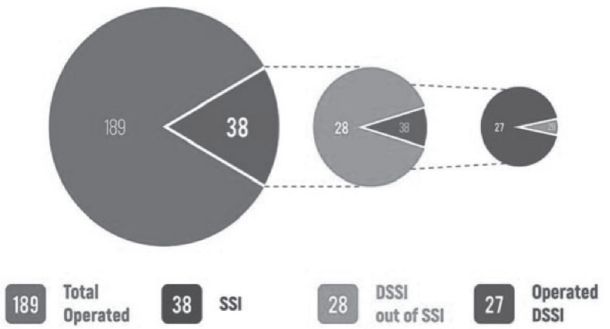

Figure-4. Infectious complications post-RC

An article by Yuuki Kyoda compares the incidence of SSI by modifying the perioperative management of surgical wound with a previous study.[23] The study shows the modification of perioperative management for the surgical wound was partly responsible for the reduction of the incidence of SSI. A study published in "Transl Androl Urol." shows the promising effects of AP in minimizing post-operative infections especially urinary tract infection (UTI) after RC.[24] The study focuses on UTI only and other complications which can affect the success of operation remains unknown.

Tzortzis Vassilios in his article find the superiority of stapler devices in obese and overweight patients in reducing RC complications as compared to standard suture technique.[25] Article by Carlo Pavone in Urologia Journal shows the post-operative complications and 90-day mortality in RC patients is significantly higher for high risk patients.[26]

In a recent study "Recovery from Cystectomy; Patients perspective" we were intrigued to find that patients are often unaware of the potential complications that may arise after RC like surgical site and urinary tract infection.[27] The study focuses mainly on challenges, decision making and self-care in patients undergoing RC.

A study in BJUI describes the asymptomatic bacteriuria (ABU), UTI and the inflammatory response, in absence of raised inflammatory indices and symptoms suggesting a redefinition of ABU and UTI in patients with an orthotopic neobladder.[28] The study challenges the current treatment protocol in diagnosing ABU and UTI in patients with ileal orthopic neobladder.

Article by Tanaka M. investigates postoperative infectious complications and found that patients who had received tobramycin and vancomycin had far less complications than in those who had received kanamycin alone.[29] A diagnosis of bladder cancer is stressful and the patient needs a clear pre and post-operative treatment plan determined by the clinician. A review article by Alberto Martini revise the pathophysiology of complications related to bowel's mucosal properties.[30] Another article discusses the importance of multidisciplinary meetings in the management of muscle invasive bladder cancer.[31] As RC is a highly morbid procedure, surgeon should consider the conditions and complications to tailor the best surgery to each patient.

Why antibiotic prophylaxis is important?

An article by Joshua K. Calvert evaluated practice patterns of AP in genitourinary surgery and assessed the impact of antibiotic prophylaxis on hospital acquired infections.[32] Another article by

del Rio G compares the AP of 3 antimicrobial regimes and their efficacy in the post-operative period.[33] These articles focus on the minimum use of antibiotics while criteria and dosage of AP is not clear as it depends on clinical decision. Overuse of antibiotic leads to resistance and hospital acquired C. difficile colitis. Therefore, clinicians are being encouraged for evidence based approaches to postoperative care.

An article by Joseph J. Pariser M.D found that culture-directed antimicrobial prophylaxis, with antifungal coverage, decreased postoperative infections.[34] The study is conducted at one institution only with significant decrease in postoperative infectious complications with the new broad spectrum AP regime. However, another population based analysis by Ross E. Krasnow identify AP regimens with the lowest incidence of infectious events after RC.[35]

A study published by Gregory W.J. Hawryluk in PLoS One Journal is a prospective observational study which describes AP for surgical procedures and its role in minimizing post-operative adverse effects.[36] The study includes all patients more than 18 years old undergoing different surgical procedures but has excluded only urology procedures.

A study published in Urol Oncol journal offers in depth insight of a diverse group of patients in which AP have reduced the incidence of UTI thus preventing them from subsequent risk of readmission due to sepsis.[37] Another study acknowledges the use of tazobactam–piperacillin (1:4 ratio) as short term AP for prevention of postoperative infections after radical cystectomy.[38] (Table-I).

Article in Urol Oncol acknowledges the importance of antibiotic during pre-operative period in reducing UTI which accounts for major infectious complication while the latter asses the efficacy of a single broad spectrum antibiotic only.

No of patients	35
Total Postoperative Bacterial Infection Rate	7 (20%)
SSI	2 (5.7%)

Table-I. Post-radical cystectomy Infections.

Lessons Learned

Our study may have limitations due to its retrospective character, including the fact that it only analyzed English-language publications, human studies, varying surgical experience, and various management protocols from various healthcare facilities. When it comes to radical cystectomy, AP vary greatly. Because RC is a very complex and morbid surgery, published guidelines are not being followed.

Since most studies indicate a shorter hospital stay and fewer infectious problems, AP is typically advised for RC with an ileal conduit. More clinical research is necessary for RC with orthotopic ileal neobladder because ileal mucosa has immunological tolerance against antigen, which results in urine that is bacteriostatic and has a large concentration of bacterial colonies without any indication of infection. Thus, we suggest not to use AP for patients who presents with bacteriuria having orthotopic ileal neobladder even if the urine culture is positive unless the patient is symptomatic (stones, sepsis and reflux). The ideal antibiotic regimen for prophylaxis requires further study and clinical trial to optimize perioperative and postoperative outcomes.

Analysis

Many patients who underwent RC continue to receive post-operative AP depending on the clinician assessment since it's a very morbid and complex procedure. The aim of this review article is to develop a preoperative AP predictive model in the form of guidelines that shows the risks and complication of patients undergoing RC. The model can be used to identify patients at high risk of postoperative complications by physicians and surgeons. We encourage other centers to conduct clinical trials regarding the importance of AP for post-radical cystectomy patients.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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AUTHORSHIP AND CONTRIBUTION DECLARATION	
1	**Musab Umair Khalid:** Substantial contribution to conception, design of the work, the acquisition, analysis.
2	**Badar Murtaza:** Substantial, contribution to conception or design of the work.
3	**Muhammad Nouman Khan:** Drafting of the work, revision it critically for important intellectual content.
4	**Aneela Shabbir:** Final approval of the version to be published.
5	**Adnan Ali:** Agreement to be accountable for all aspects of the work in ensuring that question related to the accuracy.
6	**Chaudhary Ammar Bashir:** Integrity of any part of the work are appropriately investigated and resolved.