Editorial Commentary

Urinary tract infections in patients undergoing radical cystectomy and urinary diversion: challenges and considerations in antibiotic prophylaxis

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Radical cystectomy represents the standard of care for muscle-invasive bladder cancer. Different surgical techniques of urinary diversion have been advocated during the last years. The three primary techniques of substituting the excised bladder include the non-continent urinary diversions, the continent non-orthotopic urinary diversions, and the orthotopic urinary diversions (1). While the non-continent forms have been traditionally used, continent diversions have started gaining ground in high case volume hospitals (2). When compared to the non-continent diversions, orthotopic ones confer various advantages such as a resemblance to the native bladder, enhanced functional outcomes, less psychological burden, and better quality of life (2).

Urinary diversions are technically demanding and particularly challenging for the surgeon, involving many short- and long-term complications (1). Urinary tract infections (UTIs) are among the most prominent and usually associated with substantial morbidity (3). In the current body of literature, many authors have attempted to describe various characteristics of UTIs following radical cystectomy (RC) namely, incidence, etiological factors, clinical predictors, adequacy, as well as type and susceptibility patterns of antimicrobial regimens (3-9). *Escherichia coli* is generally the most widely isolated organism in urine cultures within the first months after surgery in patients treated with orthotopic neobladder (ONB) and continent cutaneous diversion, while mixed populations of Gram-negative and Gram-positive pathogens can be isolated in ileal conduit (IC) reconstructions (3).

One consideration that should be taken into account is that patients with urinary diversions frequently become colonized (1). Besides, it is possible that patients may have previously received multiple courses of antibiotics for presumed UTIs, and may thereby have been particularly susceptible to fungal infections (10). For that reason, initial broad-spectrum coverage, including consideration of anti-fungal therapy, may be necessary (8).

Asymptomatic bacteriuria also raises considerable concern. Patients with urinary diversions have no benefit in asymptomatic bacteriuria treatment. Furthermore, deliberate colonization with an asymptomatic bacteriuria strain (*Escherichia Coli* 83972) has proved protective against symptomatic recurrences in these patient groups who do not spontaneously develop asymptomatic bacteriuria (11,12). Screening and treatment of asymptomatic bacteriuria in these patient groups are therefore, not recommended.

In a recent published multicentric series of patients who

had undergone RC, Haider *et al.* (4) assessed the rate of UTIs, the characteristics of the pathogens involved, the type and duration of antibiotics used, and the clinical risk factors incriminated. The authors reviewed 217 patients between 2009 and 2015, and found *Enterococcus* to be the most common bacterial agent in post-operative urine cultures, followed by *Klebsiella pneumoniae* and *Escherichia coli*. Given the well-known resistance patterns of enterococci to the most commonly used antibiotics, the authors highlighted the importance of developing further antibiotic regimens, especially for high-risk patients. Also, the continent type of diversion was found to be an independent risk factor for developing UTI in contrast to perioperative antibiotic prophylaxis. They commented that prolonged duration of antibiotic therapy did not result in a reduction of UTIs; hence they suggested that the administration of short prophylaxis would be preferable in such cases. More importantly, they emphasized that future treatment strategies should be more focused on the appropriate selection of antibiotics and the right use of therapeutic regimens targeted against enterococci (4).

In the non-continent diversions, yeast colonize mucus and urine during the first ten postoperative days and while the patient is under antibiotic coverage (1). Subsequently, a mixed population of yeast and gram-positive cocci such as *Streptococcus* species, *Staphylococcus epidermidis*, and enterococci develops in the conduit. After antibiotic withdrawal, gram-negative organisms including *Escherichia coli*, *Proteus*, *Pseudomonas*, and *Klebsiella* species, colonize the mixed microbial flora (1,3). Acute or recurrent pyelonephritis and sepsis are the types of UTIs which mostly predominate in these diversions (1). As conduit urine is bacteriuric in most cases, antibiotic coverage poses a dilemma and treatment should be instituted if symptoms indicate upper or lower urinary tract infection. Prophylactic treatment should be reserved for patients with a history of recurrent pyelonephritis (1).

Interestingly, deterioration of the upper tracts appears likely when urine cultures are positive for *Proteus* or *Pseudomonas* (13). Reflux, which depends on the intraluminal pressure of the conduit and the construction of the anastomosis, can also have a detrimental impact on renal function (1). Previously, Kristjánsson *et al.* emphasized the importance of anti-reflux ureteric anastomosis in preventing bacteriuria and ascending infections compared to refluxing ureterointestinal anastomoses (14).

In intestinal pouches, *Escherichia coli* is the most frequently isolated microorganism, although other Enterobacteriaceae and gram-positive cocci are also encountered (3). Again, in asymptomatic cases, antibiotic treatment should not be instituted (1). It seems that chronic bacteriuria may be a consequence of intermittent self-catheterization in these patients, while the antireflux mechanism plays a key role in preventing clinical episodes of pyelonephritis. In other forms of continent non-orthotopic diversions, such as ureterosigmoidostomies rectal urine are abundant in bacterial flora in all the patients (1).

In orthotopic continent diversions, an increased risk of UTIs is evidenced due to the easier bacterial colonization of the bowel epithelium (1). Neobladder-related UTIs are mostly implicated by *Escherichia coli* (1,3). *Pseudomonas aeruginosa* can also be found, even in a percentage equal to that of *Escherichia coli*, as it was demonstrated in a review of 79 patients treated with ONB diversion (15). Inadequate bladder evacuation and subsequent increased post-void residual volume of urine promotes bacterial colonization and increases the bacterial burden (1). Excessive mucus production by the bowel epithelium acts synergistically to an established infection, causing hindrances in the adequate clearance of microorganisms (1).

The type of bacterial population might also be influenced by the incomplete bowel preparation, resulting in residual microbial flora in the ileal or colonic segment of the neobladder (6). This assumption was judged by authors who noted a higher incidence of UTIs in ileal compared to colonic neobladders (15,16). Large *et al.* compared two groups of patients undergoing RC and IC or ONB diversion with and without bowel preparation. They found that omitting bowel preparation did not increase the rate of post-operative UTIs (17).

The association between the rate of post-operative UTIs and certain types of diversion remains debatable. Some authors mention no significant difference in the type of diversion and the risk of UTI development (3,18). However, other groups reported continent diversion to be a significant risk factor for UTIs (4,8,9). In 2018, Mano *et al.* reported a significantly higher rate of UTIs in patients undergoing ONB reconstruction especially during the first three post-operative months, and then comparable to ileal conduit during subsequent follow-up (7). Hence, more research is warranted to shed light on UTIs and different types of urinary diversion.

Yong *et al.* summarized all the available evidence regarding the best way of improving or replacing the function of the lower urinary tract using intestinal segments when the bladder had to be removed or when it had been

rendered useless or dangerous by disease. They found no statistically significant differences in the incidence of upper UTI, ureterointestinal stenosis and renal deterioration in the comparison of continent diversion with conduit diversion. They concluded that there was no evidence that bladder replacement (orthotopic or continent diversion) was better than conduit diversion following RC for cancer (19).

While the risk of UTIs in individual types of diversion needs to be further clarified, the duration of antibiotic therapy remains controversial. The absence of strict adherence to best practice policy on urologic antibiotic prophylaxis is well-documented in the existing literature (20). We recognize that compliance rates remain low, while there is a proclivity for a long duration of antibiotic treatment in selected series (21,22). Haider *et al.* reported a median duration of administration of 7 days (4). Previously, Hara *et al.* compared the duration of perioperative prophylaxis in patients treated with RC and IC diversion and did not notice significant differences in terms of post-operative febrile UTIs. They stated that the one-day prophylaxis had equivalent efficacy to that of the standard recommended protocol in preventing septic complications (5).

Particular reference should be made to the Enhanced Recovery After Surgery (ERAS) protocols. The latter represents a concept of standardized perioperative approach aiming to reduce perioperative complication rates. These multimodal care pathways have been thoroughly studied in colorectal surgery (23). In 2017, Altobelli *et al.* indicated enterococci as the most common cause of UTIs, in approximately 60% of patients readmitted during the first 90 days after RC. Readmission rates remained stable, with an incidence of 27% in the post-ERAS group versus 30% in the pre-ERAS group, though still significant. Moreover, a higher incidence of UTIs (P=0.037) in the post-ERAS readmissions was noted (24). Notwithstanding those above, we recognize the paucity of critical data for UTIs in the post-ERAS era. For that reason, we advise for future prospective studies elucidating any possible interventions based on decreasing the incidence of postoperative infections and the rates of readmissions.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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