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Review Article

Optimizing Antibiotic Prophylaxis in Transurethral Resection of Bladder Tumors: Individualized Approaches and Future Direction

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Abstract:

Our findings consist of the importance of an individualized approach based on infectious risk and prudent antibiotic management to prevent antibiotic resistance, and highlight the need for further research to better assess the clinical impact of antibiotic prophylaxis in this specific context of transurethral resection of bladder tumor.

Keywords: artificial intelligence; urology; medical training; learning; technological advances

Introduction

Antibioprophylaxis in surgery refers to the preventive administration of an antibiotic before potential contamination occurs due to a risky situation secondary to a surgical procedure. According to the Société Française d'Anesthésie et de Réanimation (SFAR) [1], antibioprophylaxis is defined as "the administration of an antimicrobial agent before, during, or immediately after a surgical procedure to prevent surgical site infection."

The Centers for Disease Control and Prevention (CDC) [2] in the United States describes antibioprophylaxis as "the use of antimicrobial drugs before exposure to pathogens, with the primary goal of preventing a potential infection, particularly in cases of surgical procedures where the risk of infection is significant."

This approach is designed to reduce the bacterial load at the surgical site. The antibiotic is administered prophylactically to create an effective therapeutic concentration in the tissues before exposure to pathogens, thereby minimizing the risk of infection associated with the surgical act.

This practice is particularly important in interventions where the risk of infection is high, especially in urological surgeries involving manipulations of the bladder, such as prolapse repair, macroplastique injections, or partial or total cystectomies, where post-operative urinary infections can be frequent and severe.

This study focuses on the importance of antibioprophylaxis in managing non-muscle-invasive bladder tumors requiring transurethral resection of the bladder (TURB). According to the 2022-2024 recommendations of the Association Française d'Urologie (AFU) [3], the incidence of bladder tumors is 2.7 million cases per year, with an annual increase of 1%. Bladder tumors represent the second most frequent urological cancer after prostate cancer and are responsible for 3% of cancer deaths.

Transurethral resection of the bladder is the standard procedure for treating non-muscle-invasive bladder tumors. This intervention, although necessary for tumor resection, carries a risk of infectious complications, particularly post-operative urinary infections [4]. The use of antibioprophylaxis aims to reduce these risks by decreasing bacterial colonization and subsequent infections.

The primary objective of this review of litterature is to determine the effectiveness of antibioprophylaxis in reducing post-operative infections in patients undergoing TURB for non-muscle-invasive bladder tumors. Based on clinical, biological, paraclinical, and cystoscopic data, in light of current recommendations, this research aims to provide additional evidence to optimize treatment protocols and improve clinical outcomes for patients with this form of bladder cancer.

I. Urothelial Tumors

Urothelial tumors, which represent more than 90% of bladder and urinary tract tumors, are similar throughout the entire height of the urinary tract. They result from a multifocal urothelial disease that can manifest in the same patient, either concurrently or successively, in the bladder, urethra, ureter, and pyelocaliceal cavities. Although morphologically similar, these tumors exhibit variable progression.

A. Pathological Presentation

Urothelial tumors can initially present in three anatomical and clinical forms:

- **In 65 to 70% of cases**, urothelial tumors have a macroscopically papillary appearance (either infiltrating the lamina propria or not). These tumors can be solitary or multiple and exhibit variable malignancy potential. Their propensity to recur and progress by infiltrating the bladder wall illustrates this variability.
- **In 30% of cases**, the tumor presents as an invasive carcinoma from the outset. These lesions often follow unnoticed flat carcinoma in situ (CIS) lesions. In both situations, the urologist performs a resection of the lesions observed during cystoscopy, and histological analysis will establish the diagnosis.
- **In a small number of cases (less than 5%)**, the disease is initially discovered at the stage of isolated carcinoma in situ (CIS). These lesions are not always clearly visible during cystoscopy but are easily diagnosed by examining urinary cytology, which reveals highly atypical high-grade tumor cells.

B. History of Classifications

From 1973 and for over 20 years, the 1973 WHO classification by Mostofi dominated, with only minor modifications. This classification divided tumors into three groups: G1, G2, and G3.

In March 1998, a meeting of pathologists, oncologists, and urologists was held to define a consensual classification for bladder tumors and flat lesions. This classification, adopted by the WHO, was published under the term WHO/ISUP 1998 classification. This new classification sparked numerous criticisms, particularly because it introduced, for the first time, the term Papillary Urothelial Neoplasm of Low Malignant Potential (PUNLMP), in addition to the categories of low-grade and high-grade carcinomas.

In 2004, the WHO and the Armed Forces Institute of Pathology (AFIP) agreed to jointly publish a classification based on the ISUP 1998 classification, in the WHO book titled "WHO Blue Book." The WHO/ISUP 2004 classification also clarified the issue of flat mucosal lesions associated or not with a tumor.

In 2016, the WHO published a new classification of urothelial tumors, more precise than the 2004 classification. This classification allows for the distribution of patients into different prognostic groups, leading to appropriate therapeutic management.

The new 2022 WHO classification [3] introduces certain modifications:

- Papillary Urothelial Neoplasms of Low Malignant Potential (PUNLMP) are retained alongside non-invasive papillary urothelial carcinomas of low grade (LG) and high grade (HG). The grade remains defined according to the 2004 WHO criteria. According to the 2022 WHO, tumors are defined as high-grade carcinomas (HG) if they have an HG component of ≥ 5%. When the HG component is < 5%, the tumor is considered low grade (LG).
- For invasive urothelial carcinomas (UC), the 2022 WHO classification recommends using the names of histological subtypes or UC with divergent differentiation, abandoning the term "variant." These subtypes must be reported as a percentage.

C. TNM Classification (p and yp*) [3].

Table 1 TNM 2017 classification of bladder cancer.

Stage T	Description	Designation
pTa	Variable grade papillary carcinoma without lamina propria invasion	**NMIBC**
pTis	High-grade non-invasive flat tumour - carcinoma in situ	
pT1	Variable grade papillary carcinoma with lamina propria invasion but no muscle invasion	
pT2	Tumour invades muscularis propria *pT2a* Tumour invades superficial muscularis propria (inner half) *pT2b* Tumour invades deep muscularis propria (outer half)	**MIBC**
pT3	Tumour invades perivesical tissue *pT3a* Microscopically *pT3b* Macroscopically (extravesical mass)	
pT4	Tumour invades any of the following: prostate stroma, seminal vesicles, uterus, vagina, pelvic wall or abdominal wall. *T4a* Prostate stroma, seminal vesicles, vagina or uterus *T4b* Pelvic wall or abdominal wall	

N Regional lymph nodes

Nx Regional lymph nodes cannot be assessed

N0 *No regional lymph node metastasis*

N1 *Metastasis in a single lymph node in the true pelvis (hypogastric, obturator, external iliac, or presacral)*

N2 *Metastasis in multiple lymph nodes in the true pelvis (hypogastric, obturator, external iliac, or presacral)*

N3 *Metastasis in one (or more) common iliac lymph node(s)*

Distant metastasis

M0 *No distant metastasis*

M1 *Distant metastasis*

- ***M1a: non-regional lymph node metastasis(es)***
- ***M1b: other distant metastasis (es)***

**** yp: y: stage reassessed after neoadjuvant therapy (chemotherapy or radiotherapy)***

II Nosocomial Infections and Urological Interventions

a. Infectious Risk in Urological Surgery

The first question to address is whether there is a link between urinary tract infections and urological interventions. The answer is yes. This phenomenon has been known for over 140 years and was elegantly described by Sir Andrew Clark in The Lancet in 1883, reporting the association between urethral catheterization and fever, termed catheter fever [4].

Healthcare-associated infections are summarized in Table 1. What urologists fear the most are deep surgical site infections (SSI), complicated urinary infections (UTIs), pyelonephritis, and septicemia, all of which pose a threat to the patient and incur increased costs for society.

b. Minimally Invasive Diagnostic Interventions

Transrectal ultrasound-guided prostate biopsy was one of the most frequent diagnostic tools in urology, although it has been replaced by transperineal biopsy in the latest EAU recommendations [5] primarily aimed at diagnosing prostate cancer. This is a quick and minimally invasive procedure but is associated with a relatively high risk of infection [6], whereas the transperineal approach carries a lower risk.

Cystoscopy, another common minimally invasive diagnostic tool, rarely leads to infectious complications [1].

c. Invasive Endourological Interventions

Transurethral resection of the prostate (TURP), one of the main transurethral operations, has been the subject of several controlled studies over the past four decades. In a 2006 meta-analysis, Jens Rassweiler et al. [7] found an average urinary infection rate between 1.7% and 8.2%, and a mortality rate between 0% and 0.25%.

Ureteroscopy and percutaneous nephrolithotomy (PCNL) are associated with infectious complications in 2.4%-40.4% of cases. These high rates seem linked to the difficulty level of the intervention and potentially the fact that these procedures are performed under relatively high pressure in the urinary tract.

In a multicenter randomized controlled trial from September 17, 2017, to December 31, 2019, in five hospitals in Germany, it was concluded that the infection risk associated with TURB is 3%, regardless of whether or not antibioprophylaxis is used [8].

d. Urological Surgical Interventions

Surgical interventions performed by laparoscopy or open surgery are divided into clean, clean-contaminated, contaminated, and infected procedures with an expected SSI risk of about 2%, 8%, 15%, and 40%, respectively [9, 10]. In studies on the implantation of urological devices such as penile prostheses and artificial urinary sphincters, infection rates vary from 1% to 17% [11].

e. Patient-Specific Risk Factors

The characteristics and risks vary significantly from patient to patient. Thorough medical history and detailed clinical examination help reveal the patient's general physical condition before surgery and stratify the risk. It is essential to characterize the patient based on endogenous and exogenous risk factors. General risk factors for infectious complications include advanced age, poor nutritional status, diabetes mellitus, smoking, obesity, coexisting remote infections, and colonization by microorganisms [12].

f. Specific Risk Factors for Bladder Tumors Requiring TURB

In a study conducted in Japan [12], including 687 patients who underwent TURB between 2006 and 2017 at Hiroshima Prefectural Hospital, post-operative urinary tract infections were defined as febrile urinary infections (≥38°C). Antibioprophylaxis before TURB was primarily first-generation cephalosporins. The identified risk factors for post-operative infections were previous pelvic radiotherapy, age, preoperative hospital stay, tumor size, as well as pyuria and bacteriuria.

I. Mechanism of Contamination and consequences

a. Pathogenesis

The contamination of the surgical site mainly occurs in the perioperative period. Microorganisms usually originate from the patient themselves, either already present at the surgical site (in clean-contaminated or higher contamination class surgeries) or from their skin flora (in clean surgeries). These microorganisms can produce toxins and other substances that enhance their ability to invade and destroy host tissues.

For example, many Gram-negative bacteria produce endotoxins that stimulate cytokine production, potentially leading to a systemic inflammatory response syndrome and causing multiple organ failure [1, 2].

b. Sources of Contamination

The contamination of the surgical site mainly develops during surgery and can be acquired from endogenous or exogenous sources.

The endogenous source is the most frequent cause of surgical site infections (SSI). The microbial flora may be present either at or distant from the surgical site. Staphylococcus aureus and coagulase-negative staphylococci are the two most frequently encountered microorganisms, being part of the resident skin and mucosal flora, presenting a high risk of contamination [13].

The exogenous origin includes the flora of the personnel and the surgical team, the operating room environment, and the equipment used during the intervention. This origin is less frequent due to the reinforcement of aseptic rules and the use of single-use sterile equipment. The exogenous flora is mainly composed of anaerobes and Gram-positive bacteria (Staphylococcus and Streptococcus) [14].

Fungal contaminations are rare, whether of endogenous or exogenous origin, and their pathogenicity is not yet fully understood.

c. Consequences of Infections

1) Morbidity and Mortality

Post-operative infections play a crucial role in morbidity and mortality among patients undergoing surgical interventions. Patients with SSIs can experience a range of complications, from mild to potentially life-threatening [15]. These complications can range from discomfort and pain to life-threatening situations, such as sepsis and multiple organ failure [16].

Studies have shown that patients with SSIs have a higher mortality rate compared to those without infections [16, 17]. Additionally, the presence of an infection can delays the resumption of adjuvant treatments in certain oncological situations, such as chemotherapy or immunotherapy, which can compromise disease control and long-term survival of patients.

2) Impact on Hospital Stay and Healthcare Costs

Post-operative infections also increase the length of hospital stay for patients. SSIs can prolong the hospital stay from several days to several weeks, not only affecting patient recovery but also significantly increasing healthcare costs. According to a study by Kirkland et al. [18], patients with SSIs had an average hospital stay of 9.7 days longer than those without infection. Furthermore, the cost of care for SSIs is substantial, including the cost of antibiotics, intensive care, and sometimes repeated surgical interventions to manage complications [19].

V. Principles of Antibiotic Prophylaxis

a. Objective

Antibiotic prophylaxis, which involves administering antibiotics before or during surgery to prevent infections, is a widespread practice. It is particularly used during surgeries that pose a risk of bacterial dissemination, as a precautionary measure to reduce postoperative infections. However, its use must be balanced to limit the development of resistant bacterial strains, while considering the associated risks of infections.

Despite being widely practiced, some uncertainties persist regarding the efficacy and modalities of antibiotic prophylaxis. Therefore, a thorough evaluation of the scientific evidence supporting this practice is necessary to better understand its clinical implications and optimize its use in surgical interventions.

Our study aims to evaluate the practice of antibiotic prophylaxis in endoscopic surgery for bladder tumors. The objective is to determine if there are deviations from international standards and, if so, to propose corrective measures to improve existing protocols and optimize clinical outcomes.

b. Prescription Rules for Antibiotic Prophylaxis in Urological Surgery

In this section, we will discuss the current rules and recommendations for antibiotic prophylaxis, particularly those applied to urological surgery, and then review the latest recommendations from various scientific societies on antibiotic prophylaxis in bladder tumors:

- The selected antibiotic must be specific to the surgical intervention and target the germs commonly encountered in this type of procedure [20]. Antibiotic prophylaxis protocols do not aim to be effective against all microorganisms but rather to target a specific and restricted bacterial range [21, 22].
- Monotherapy is recommended [1, 2].
- Each team should establish a written protocol identifying the practitioner responsible for prescribing and monitoring antibiotic prophylaxis. This responsibility may fall to the anesthesiologist-resuscitator or the surgeon [1, 23].
- Preference should be given to molecules not used in therapeutic treatments to limit the risk of resistance and preserve the efficacy of curative treatments. First- or second-generation cephalosporins (whose spectrum mainly targets Gram-negative bacilli) meet these criteria well in urology [1, 2].
- The chosen molecule should have as narrow a spectrum of action as possible to limit the emergence of resistances and minimize the impact on the patient's bacterial flora [1].
- It is recommended to administer antibiotic prophylaxis with cephalosporin (or alternatives in case of allergy, except vancomycin) no earlier than 60 minutes before and no later than before the start of the intervention to reduce the incidence of SSIs [1, 24, 25].
- It is advisable to re-administer one or more doses of intraoperative antibiotic prophylaxis in case of prolonged surgery to reduce the risk of SSIs [1, 26, 27].
- Increasing the unit dose of cephalosporin used in antibiotic prophylaxis in obese patients is unlikely to be recommended to reduce the incidence of SSIs, except in specific cases (BMI over 50 kg/m²) [1, 28, 29].
- It is generally discouraged to continue administering antibiotic prophylaxis after the end of the surgical intervention in the vast majority of situations [1, 30, 31].

The use of antibiotic prophylaxis is not without consequences, including increased resistance, alterations in the patient's bacterial flora, and risks of toxic effects, particularly allergic reactions. Therefore, strict rules govern its use. The main ones include respecting specific indications limited to certain surgical interventions, choosing molecules targeting present germs different from those used in curative treatments, and starting prophylaxis immediately before the intervention.

VI. Current Recommendations

In this chapter, we will discuss the current recommendations issued by scientific societies, such as the European Association of Urology (EAU), the American Urological Association (AUA), and other relevant organizations. These recommendations provide essential guidelines for managing patients with bladder tumors and define standard protocols for TURBT in this context.

Urologic surgeons must prioritize and rigorously maintain an aseptic environment to minimize the risk of infections from endogenous (patient's microbiome) and exogenous (nosocomial) sources. This involves using appropriate methods for cleaning and sterilizing instruments, regular and thorough cleaning protocols for operating rooms and recovery areas. They must also be aware of the local prevalence of pathogens for each type of procedure, their antibiotic sensitivity profiles, and virulence to establish local written guidelines [32].

The available evidence has allowed the panel to make recommendations regarding transurethral resection of the bladder.

According to the EAU 2024 guidelines, antibiotic prophylaxis is not necessary for patients undergoing transurethral resection of the bladder (TURB), except for those at high risk of postoperative infection. High-risk patients include those with a history of recurrent urinary tract infections, multiple previous interventions, immunosuppression, or anatomical anomalies predisposing to infections. For these patients, prophylaxis with cephalosporins or aminopenicillins with beta-lactamase inhibitors is recommended.

The formalized recommendations from the SFAR, in association with the Société de Pathologie Infectieuse de Langue Française (SPILF) and the Association Française d'Urologie (AFU), are summarized in their directive synthesis titled "Antibioprophylaxie en chirurgie et médecine interventionnelle 2.0" dated 22/05/2024 [1].

The working group decided not to include in these recommendations the interest of screening by urine culture and treating urinary colonization before urological surgery. The current recommendations focus solely on antibiotic prophylaxis, which will be systematically administered when indicated, regardless of the use of preoperative curative antibiotic therapy.

For TURB, the recommendations indicate that routine antibiotic prophylaxis is not necessary. Exceptions include patients at high risk of postoperative infection, for whom appropriate antibiotic prophylaxis should be considered.

In their fifth revision of the "Best Practice Statement," published in February 2020, the American association of Urology (AUA) recommends antibiotic prophylaxis with fluoroquinolone or trimethoprim/sulfamethoxazole. They consider TURP and TURB as similar procedures (cystourethroscopy with manipulation).

The Canadian Association of Urology (CUA)'s recommendations on antibiotic prophylaxis for urological procedures were published in 2015. A panel of eight experts conducted a literature search in Embase, Medline, and other evidence-based medical reviews to identify suitable systematic reviews. The panel performed its own systematic review. Inclusion was limited to studies where patients had no known infection before the procedure. The CUA groups TURB with cystoscopy and recommends prophylaxis only for high-risk patients [33].

The Essential Japanese Guidelines for the Prevention of Perioperative Infections in the Urological Field (JUA) were first published in 2007, with an update in 2015 [34]. The JUA recommends the use of antibiotic prophylaxis before a transurethral resection of the bladder tumor (TURBT) for patients at high risk of infection. However, it specifies that patients at low risk of infection do not require antibiotic prophylaxis.

VII. Clinical Studies on the Efficacy of Antibiotic Prophylaxis

In a multicenter randomized controlled trial conducted from September 17, 2017, to December 31, 2019, across 5 hospitals in Germany [8], 459 patients were included in the multivariable analysis. Among them, 202 out of 459 (44.1%) received antibiotic prophylaxis before transurethral resection of the bladder tumor (TURBT), while 257 out of 459 (55.9%) did not receive prophylaxis. The antibiotics administered were fluoroquinolones in 135/202 (66.8%) cases, cefazolin in 60/202 (29.7%), and amikacin in 7/202 (3.5%) patients. There was no difference in antibiotic-related complications observed between the cohorts.

It is important to note that all patients included in the trial had negative urine cytobacteriological study and no bladder or ureteral catheter preoperatively.

Among patients without antibiotic prophylaxis, 6 out of 202 (2.9%) developed postoperative fever, compared to 8 out of 257 (3.1%) in the prophylaxis group. None of the patients with postoperative fever developed septicemia, defined by fever associated with hypotension or elevated lactate levels.

In the prophylaxis group, 3 out of 6 patients (50%) developed fever during hospitalization and 3 out of 6 after discharge. In the non-prophylaxis group, 6 out of 8 patients (75%) had postoperative fever during hospitalization and 2 out of 8 (25%) after discharge.

These data confirm the non-inferiority of omitting antibiotic prophylaxis under these conditions.

In 1988, McDermott randomized 91 patients, among whom 44 received antibiotic prophylaxis and 47 did not. Documented bacteriuria (>100,000 bacteria/mL) was the primary outcome measure. The results showed a statistically non-significant advantage favoring antibiotic prophylaxis in reducing biochemical infections [34].

In 1993, Delavierre conducted a randomized controlled trial involving 61 patients: 32 received a single dose of Pefloxacin and 29 received a placebo, with bacteriuria as the primary outcome measure. Among patients in the Pefloxacin group, 3 out of 32 (9.4%) developed postoperative bacteriuria, compared to 7 out of 29 (24.1%) in the placebo group, a difference that was not statistically significant. No patient developed symptomatic urinary tract infection, leading the authors to conclude that antibiotic prophylaxis is not indicated for TURBT [35].

Bootsma in 2008 included these two randomized controlled trials in a systematic review of antibiotic prophylaxis in urological procedures. He concluded that these moderate to low-level evidence suggests that antibiotic prophylaxis is not necessary for TURBT and highlights a lack of well-conducted studies in this context [36].

Wagenlehner in a randomized study in 2005 also emphasized the debate surrounding postoperative bacteriuria as the key parameter for defining the efficacy of antibiotic prophylaxis [37].

Verzotti conducted a retrospective review of 753 transurethral resection of bladder tumor (TURBT) procedures. Among the patients, 599 out of 753 (79.5%) did not receive antibiotic prophylaxis, and 31 out of 599 (4.1%) developed an infectious complication. In contrast, 20.4% (154/753) of patients received antibiotic prophylaxis, and 7.14% (11/154) of them experienced an infectious complication. A significant correlation was observed between antibiotic prophylaxis and the development of postoperative infections. The authors concluded that antibiotic prophylaxis in TURBT is unnecessary [38].

A retrospective analysis by Kohada examined the use of antibiotic prophylaxis in transurethral bladder tumor resection (TURBT) among 687 patients between 2006 and 2017. Cefazolin was primarily used as antibiotic prophylaxis, and 21 patients (3.1%) suffered from postoperative urinary tract infection (UTI). Univariate analysis showed that tumor size (≥2 cm) and age (≥75 years) were associated with postoperative UTIs [39].

Conclusion: The debate over antibiotic prophylaxis in TURBT remains contentious despite extensive research. Studies reviewed here suggest that while antibiotic prophylaxis may reduce the risk of postoperative infections, its routine use may not be justified in all cases. Further research, particularly large-scale randomized controlled trials, is warranted to establish clear guidelines tailored to different patient profiles and procedural contexts in TURBT.

List of tables:

Table 1: 2017 TNM classification of Bladder Cancer

Conflict Of Interest: NONE

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