



## Antimicrobial Prophylaxis in Urological Surgery

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Surgical site infection (SSI) is defined as an infection occurring within one month from surgery or intervention. SSIs are classified into three categories: Clean, clean-contaminated, and contaminated. They are defined as procedures that avoid entering the urinary tract, involve entry of the urinary tract, and involve the bowels, respectively. The purpose of antimicrobial prophylaxis (AMP) is to protect the surgical wound from contamination by normal bacterial flora. AMP should be based on penicillin with beta-lactamase inhibitors, or first- or second-generation cephalosporins. Broad-spectrum antimicrobials, such as third- and fourth-generation cephalosporins or carbapenems, should be used to treat postoperative infections but not AMP. AMP should be started no less than 30 minutes prior to the start of the operation. AMP should be administered by a single dose or be terminated within 24 hours in cases of transurethral, clean, or clean-contaminated surgery, and within 2 days in cases of bowel (contaminated) surgery. These guidelines are applicable preoperatively only for non-infected, low-risk patients. The risk of patients for infection should be evaluated preoperatively, such as with a urine culture test. In cases with preoperative infection or bacteriuria that can cause an SSI or urinary tract infection following surgery, patients must receive adequate preoperative treatment based on their individual situation.

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## INTRODUCTION

Guidelines published by the Centers for Disease Control and Prevention (CDC) in 1999 are well known. These guidelines present the concept of a single-dose (including intraoperative dosing) antimicrobial prophylaxis (AMP) to prevent surgical site infections (SSIs) [1], leading to a worldwide revolution in the perioperative management.

The initial version of the Japanese guidelines for preventing perioperative infection in the field of urology was published by the Japanese Urological Association (JUA) in 2007 [2]. Thereafter, several important issues have been

established, such as the development of the criteria for use of single-dose AMP, skin disinfection, and control of hospitalized infection. Additionally, the methods used for AMP and perioperative management have radically changed. Moreover, new surgical techniques, including transurethral enucleation of the prostate (holmium laser enucleation of the prostate [HoLEP], transurethral enucleation with bipolar [TUEB] resection), brachytherapy, transurethral lithotripsy using a flexible scope, laparoscopic surgery, robotic-assisted surgery, and pelvic floor reconstruction surgery, have been introduced. These new techniques are awaiting verification as effective, perio-

perative management strategies for preventing SSI.

The new 2015 edition of the JUA guidelines [3] was designed to be consistent—as much as possible—with the international guidelines, such as those of the European Association of Urology (EAU) [4] and the American Urological Association (AUA) [5] guidelines. Herein, we summarize the essential message of the 2015 edition of JUA guidelines and discuss the controversy of preventing perioperative infection in the field of urology. Notably, these guidelines are applicable preoperatively to non-infected, low-risk patients. Those associated with preoperative local or systemic infections, including bacteriuria and bacteremia, must receive adequate preoperative treatment based on individual situation.

## GENERAL INFORMATION

### 1. Definition of Perioperative Infection

Perioperative infection is defined as an infection occurring within one month from surgery or intervention. An infection in a location near the surgical site is considered to be an SSI. This infection can be further categorized as superficial incisional, deep incisional, or organ/space SSI, according to the guidelines of the CDC [1].

### 2. Classification of Types of Surgery

The CDC guidelines classify surgery types as clean, clean-contaminated, and contaminated. The risk for occurrence of an SSI ranges from 1% to 4% in clean, 4% to 10% in clean-contaminated, and 10% to 15% in contaminated cases [4]. According to the JUA guidelines, these categories are defined as procedures that avoid entering the urinary tract, involve entry of the urinary tract, and involve the bowels, respectively (Table 1) [3], while surgeries involving the bowels are classified as

clean-contaminated in the EAU and AUA guidelines [4,5].

### 3. Preoperative Management and AMP

The purpose of AMP is to protect the surgical wound from contamination by normal bacterial flora. Therefore, AMP should be based on penicillin with beta-lactamase inhibitors (BLIs), or first- or second-generation cephalosporins (evidence level [EL]; IVa, recommendations grade [RG]; B). Broad-spectrum antimicrobials, such as third- and fourth-generation cephalosporins or carbapenems, should be used to treat postoperative infections but not AMP (EL; IVa, RG; D). AMP should be started no more than 30 minutes prior to the start of the operation for an adequate intra-tissue concentration of the antimicrobial at the surgical site [6]. In addition, AMP should be administered within the 24 hours in cases of transurethral, clean, and clean-contaminated surgeries (EL; IVa, RG; B) [7,8], and within 2 days in cases of bowel—or contaminated—surgeries (EL; IVa, RG; B) to minimize risk of developing SSI [9].

### 4. Risk Factors for SSIs

Possible risk factors for SSIs are classified into two general categories: Patient-related and medical care-related factors. Patient-related risk factors include age, low nutrition, smoking, obesity, diabetes, perioperative antimicrobial treatment, longer duration of steroid dosing, immune deficiency, and duration of preoperative hospitalization, which could be representative of the American Society of Anesthesiologists (ASA) score. On the other hand, medical care-related risk factors include the duration of surgical scrub, skin antisepsis, preoperative shaving, preoperative skin preparation, AMP, surgical time, blood loss volume, laparoscopic vs. open surgery, poor hemostasis, poor obliteration of dead space, tissue trauma, operation room ventilation, inadequate sterilization of instruments, artificial

**Table 1.** Surgical categories for urological surgery

Transurethral/endoscopic surgery
TURBT, TURP, transurethral ureterolithotripsy, percutaneous nephrolithotripsy
Open/laparoscopic surgery
Clean
Nephrectomy, adrenalectomy, partial nephrectomy, intra-abdominal lymph node dissection, inguinal or scrotum surgery
Clean-contaminated
Nephroureterectomy, prostatectomy, vesico-ureteral neostomy, partial cystectomy, cystectomy (uretero-cutaneostomy), renal transplantation
Contaminated (using bowels)
Cystectomy (ileal-conduit, neobladder), bladder augmentation

TURBT: transurethral resection of bladder tumor, TURP: transurethral resection of the prostate.

foreign body, and surgical drainage.

Reducing hospitalization is important to prevent hospital-related infections (EL; IVa, RG; B). As a part of perioperative management, blood sugar levels following the operation should be controlled to less than 200 mg/dl. Drains and catheters that are used should be the closed type and should be removed as early as possible (EL; IVa, RG; B). Neither preoperative hair shaving nor removal is necessary for any type of urological surgery (EL; II, RG; D).

## OPEN/LAPAROSCOPIC SURGERY

### 1. Categorization of Urological Open/Laparoscopic Surgery

Urological open/laparoscopic surgical procedures are categorized as follows. Clean surgery involves not entering the urinary tract, such as nephrectomy and adrenalectomy. Clean-contaminated surgery involves entry into the urinary tract, such as nephroureterectomy and prostatectomy. Contaminated surgery, such as radical cystectomy with urinary diversion, involves the bowels [2,3].

### 2. Antimicrobials and Duration of AMP Dosing

#### 1) Clean surgery

Partial nephrectomy is classified as a clean surgery because the SSI rate for this type of surgery is as low as that for other clean surgical procedures [6]. Similarly, inguinal and scrotum procedures are classified as clean surgeries, as noted in the previous version of the guidelines (EL; IVa, RG; B) [2]. The recommended AMP is a single dose of first-generation cephalosporins or penicillin with BLIs (EL; IVa, RG; B) (Table 2) [7-10].

### 2) Surgery involving entry into the urinary tract

The recommended AMP is a single dose or is terminated within 24 hours of first- or second-generation cephalosporins or penicillin with BLIs (EL; IVa, RG; B) (Table 2) [7-10].

### 3) Surgery using the bowels

AMP should be provided within the first 48 hours or less using second-generation cephalosporins, cephamycins, or penicillin with BLIs. Notably, a longer duration leads to microbial substitution phenomenon (EL; IVa, RG; B) (Table 2) [7,11,12].

## PROSTATE BRACHYTHERAPY

### 1. Preoperative Management

Reported risk factors for infection following prostate brachytherapy are shaving and preoperative urinary tract infection (UTI) [13]. Therefore, unnecessary hair cutting should be avoided, while confirmation of the absence of bacteriuria by providing appropriate antimicrobials preoperatively is also necessary (EL; IVa, RG; C2).

### 2. Antimicrobials and Duration of AMP Dosing

A multicenter research study previously conducted in Japan reported six (0.7%) patients with infection among 826 patients who underwent a prostate brachytherapy procedure [13]. AMP should be first-generation cephalosporins or penicillin with BLIs to prevent contamination by skin bacterial flora by puncture. Administration should generally be provided as a single dose. Oral fluoroquinolones, which showed good intra-prostatic drug distribution, are recommended as an alternative for AMP (EL; IVa, RG; C1) (Table 2) [4,5,13,14].

**Table 2.** AMP for open and laparoscopic urological surgery

Classification	Antimicrobials	Duration
Open/laparoscopic		
Clean	1st generation cephalosporins, or penicillins with BLIs <sup>a)</sup>	Single dose (no AMP for low risk cases)
Clean-contaminated	1st or 2nd generation cephalosporins, or penicillins with BLIs <sup>a)</sup>	Single dose or terminated within 24 hours
Contaminated (using bowels)	2nd generation cephalosporins, cephamycins, or penicillins with BLIs	Single dose or terminated within 48 hours
Prostate brachytherapy	1st generation cephalosporins, or penicillins with BLIs <sup>a)</sup> , or oral quinolones	Single dose

AMP: antimicrobial prophylaxis, BLIs: beta-lactamase inhibitors.

<sup>a)</sup>Except for tazobactam/piperacillin.

**Table 3.** AMP for transurethral endoscopic urological surgery

Classification	Antimicrobials	Duration
TURBT	1st or 2nd generation cephalosporins, or penicillins with aminoglycosides	BLIs <sup>a)</sup> , or Single dose or terminated within 24 hours <sup>b)</sup>
TURP	1st generation cephalosporins, or penicillins with aminoglycosides	BLIs <sup>a)</sup> , or Single dose or terminated within 72 hours
HoLEP/TUEB (hospitalized)	1st or 2nd generation cephalosporins or penicillins with aminoglycosides	BLIs <sup>a)</sup> , or Single dose or terminated within 48 hours
HoLEP/TUEB (outpatient surgery)	1st or 2nd generation cephalosporins, or penicillins with aminoglycosides	Single dose
Transurethral surgery for upper urinary tract	with oral quinolones or cephalosporins 1st or 2nd generation cephalosporins, or penicillins with aminoglycosides, or oral quinolones	3 days (additional dosing optional) Single dose or terminated within 24 hours

AMP: antimicrobial prophylaxis, TURBT: transurethral resection of bladder tumor, TURP: transurethral resection of the prostate, HoLEP: holmium laser enucleation of the prostate, TUEB: transurethral enucleation with bipolar, BLIs: beta-lactamase inhibitors.

<sup>a)</sup>Except tazobactam/piperacillin, <sup>b)</sup>low-risk cases without preoperative urinary tract infection can be considered to require no AMP.

## TRANSURETHRAL RESECTION OF BLADDER TUMOR

### 1. Preoperative Management

Cases with preoperative UTI should be treated and confirmed as negative for bacteriuria prior to surgery (EL; II, RG; A).

### 2. Antimicrobials and Duration of AMP Dosing

A meta-analysis showed that AMP for transurethral surgery decreased the incidence of bacteriuria, symptomatic UTI, and bacteremia [15]. Therefore, recommended AMP is a single dose or is terminated within 24 hours is recommended for patients undergoing transurethral resection of bladder tumor (EL; III, RG; B). As an option, low-risk patients can be considered as not requiring AMP (EL; III, RG; C2) (Table 3) [16].

## TRANSURETHRAL RESECTION OF THE PROSTATE (TURP)/TRANSURETHRAL ENUCLEATION OF THE PROSTATE (HOLEP, TUEB)

### 1. Preoperative Management

Patients with preoperative bacteriuria should undergo antimicrobial therapy, and its resolution should be confirmed prior to surgery (EL; II, RG; A). Patients with preoperative urinary tract catheterization are considered to be at high risk for postoperative infection, but—to the best of our knowledge—no apparent recommendations for antimicrobial use have been reported thus far in the

literature.

### 2. Antimicrobials and Duration of AMP Dosing

AMP is required to decrease the rates of postoperative fever and bacteremia following transurethral resection of the prostate (TURP) (EL; I, RG; A) [17,18]. Penicillins with BLIs or first- or second-generation cephalosporins are recommended for no longer than 72 hours (EL; III, RG; B). This is because AMP provided within 72 hours suppresses the occurrence of bacteremia more effectively than a single dose [17,18]. However, single-dose oral AMP may be considered for low-risk patients (EL; III, RG; B) [19]. Antimicrobial use at the time of catheter removal can be considered in contaminated cases (EL; III, RG; B).

In case of transurethral enucleation of the prostate (HoLEP/TUEB resection), the duration of dosing can be shorter than TURP, including a single dose (EL; IVb, RG; C1). According to the AUA guidelines, AMP should be administered for no longer than 24 hours with oral fluoroquinolones, oral sulfamethoxazole-trimethoprim (ST), or alternative antimicrobials, such as aminoglycosides, first- or second-generation cephalosporins, or penicillin with BLIs (Table 3) [5].

## TRANSURETHRAL SURGERY FOR THE UPPER URINARY TRACT

### 1. Preoperative Management

Patients with preoperative UTI should be treated with antimicrobials in advance to be free of bacteria prior to surgery (EL; II, RG; A).

## 2. Antimicrobials and Duration of AMP Dosing

AMP is considered to be required for patients undergoing transurethral surgery for the upper urinary tract. However, there is no definitive evidence regarding the duration and type of AMP. Antimicrobials, such as penicillin with BLIs, first- or second-generation cephalosporins, aminoglycosides, and quinolones, are recommended to target the most common causative bacteria, including *Escherichia coli*, followed by *Enterococcus* species and *Pseudomonas aeruginosa* (EL; III, RG; B) [20-23]. These treatments should be terminated within the first 24 hours (Table 3).

Patients without risks, such as a longer duration of percutaneous nephrostomy, placement of a ureteral stent or urethral catheter, bacteriuria, diabetes, and immunodeficiency, may be considered as candidates requiring no AMP (EL; III, RG; C2).

## URINARY TRACT STONE SURGERY

Procedures that are used for urinary stones include extracorporeal shock wave lithotripsy (SWL), percutaneous nephrolithotripsy (PCNL), and transurethral ureterolithotripsy (TUL). These procedures vary depending on the surgical approach and route of bacterial invasion. Importantly, the operative procedure and presence of preoperative bacteriuria should be considered when deciding on the appropriate AMP methodology. This is because patients who are scheduled for urinary stone surgery often have preoperative bacteriuria.

## 1. Shock Wave Lithotripsy

### 1) Risk factors for febrile UTIs

A systematic review that analyzed the findings of nine different randomized controlled trials of patients without bacteriuria prior to SWL showed that AMP is not necessary in patients without bacteriuria (EL; I, RG; D) [24]. Another systematic review demonstrated that preoperative stenting does not increase the rate of febrile UTI after SWL in patients without preoperative bacteriuria (EL; I, RG; D) [25].

In contrast, patients with large stones ( $\geq 2$  cm in diameter), infected stones, or preoperative stenting are at high risk for febrile UTI following SWL [26]. A previous study showed that patients with stones with a diameter of  $\geq 3$  cm showed a significantly higher rate of bacteriuria compared with those with renal stones with a diameter of 0.4 to 3 cm (20% vs. 10%) [27]. Struvite was also found to be associated with bacteriuria more frequently than other types of stones after SWL (17.3% vs. 2.1%) [28].

### 2) Antimicrobials and duration of AMP dosing for SWL

AMP is not required for febrile UTI. However, AMP should be considered for those with risk factors, such as preoperative bacteriuria, repeated SWL, infected stones, and stones with a size of  $\geq 2$  cm. Penicillins with BLIs, second- or third-generation cephalosporins, aminoglycosides, and oral quinolones or sulfamethoxazole/trimethoprim (ST) are recommended in patients with high risk (EL; IVa, RG; B) (Table 4).

**Table 4.** AMP for urinary stone surgery

Classification	Antimicrobials	Duration
Shock wave lithotripsy		
Low risk	None	No AMP
High risk (bacteriuria, infected stone, endoscopic manipulation, repeated SWL history of febrile urinary tract infection, stone diameter $\geq 2$ cm)	2nd or 3rd generation cephalosporins, or penicillins with BLIs <sup>a)</sup> , or aminoglycosides, or oral quinolones or sulfamethoxazole/trimethoprim	Single dose
Percutaneous nephrolithotripsy		
Low risk	1st or 2nd generation cephalosporins, or penicillins with BLIs <sup>a)</sup> , or aminoglycosides	Single dose
High risk (stone diameter $\geq 2$ cm, hydronephrosis)	1st or 2nd generation cephalosporins, or penicillins with BLIs <sup>a)</sup> , or aminoglycosides	Preoperative antimicrobial therapy
Transurethral ureterolithotripsy		
	1st or 2nd generation cephalosporins, or penicillins with BLIs <sup>a)</sup> , or aminoglycosides	Single dose

AMP: antimicrobial prophylaxis, BLIs: beta-lactamase inhibitors.

<sup>a)</sup>Except for tazobactam/piperacillin.

## 2. Percutaneous Nephrolithotripsy

### 1) Frequency of perioperative infection

The rate of postoperative infection following PCNL ranges from 3.5-10% [6,29,30]. The rates of postoperative bacteriuria and febrile UTI were 35% and 10%, respectively, when no AMP was administered in patients without preoperative bacteriuria [29].

### 2) Antimicrobials and duration of AMP dosing for PCNL

AMP is necessary for PCNL due to the high rate of febrile UTI. AMP is generally recommended as a single dose of first- or second-generation cephalosporins, penicillin with BLIs, or aminoglycosides (EL; III, RG; B). High-risk patients with stones sized  $\geq 2$  cm or hydronephrosis should be considered to undergo preoperative antimicrobial therapy for 1 week (EL; III, RG; B) (Table 4) [31,32].

## 3. Transurethral Ureterolithotripsy

### 1) Antimicrobials and duration of AMP dosing for TUL

There is insufficient evidence showing the need for AMP and the appropriate duration of dosing. A randomized controlled trial that investigated the necessity of AMP for TUL reported that a single dose of levofloxacin resulted in a lower rate of postoperative bacteriuria compared with no prophylaxis (2% vs. 13%,  $p=0.02$ ) [33]. This finding indicated that AMP as a single dose is recommended for TUL (EL; II, RG; B). According to other reports, as well as the EAU and AUA guidelines [4,5], first- or second-generation cephalosporins, penicillin with BLIs, and aminoglycosides are recommended (EL; VIa, RG; B) (Table 4).

## PROSTATE BIOPSY

In Japan, the transrectal approach is the primary choice

in 75% of cases, while a transperineal procedure is used in only approximately 25% [34]. Recently, the numbers of resistant strains have shown annual increases, resulting in an increased rate of post-biopsy infections [35], although the procedure itself can sometimes induce fatal complications [36]. Pre-biopsy management and AMP should be selected according to the modality used to approach the prostate. This is recommended because there have been reports of infection caused by quinolone-resistant strains [37], as well as extended spectrum beta-lactamase-producing bacteria [38] in patients who underwent previous prostate biopsy. Post-biopsy febrile UTI can cause severe and fatal complications. Therefore, immediate treatment with broad-spectrum antimicrobials is required when patients complain of some urinary or febrile symptoms following prostate biopsy (EL; V, RG; C1).

### 1. AMP for Transperineal Prostate Biopsy

A retrospective study conducted in Japan showed no significant difference in post-transperineal prostate biopsy infectious complications between single and several-day dosing of levofloxacin at 500 mg (0.30% vs. 0.46%) [34]. For transperineal prostate biopsy, fluoroquinolones—which have a good intra-prostate distribution—are recommended as a single-dose regimen (EL; IVb, RG; C1) (Table 5).

### 2. AMP for Transrectal Prostate Biopsy

Several randomized controlled trials have reported no significant differences regarding the occurrence of infectious complications between 1- and 3-day AMP protocols for transrectal prostate biopsy [39-41]. Furthermore, a retrospective study that was conducted in Japan also showed no significant difference in post-transrectal prostate biopsy infectious complications between single and several-day dosing (0.82% vs. 1.04%) [34]. These reports indicate that AMP with a single high dose of fluoroquinolones is recommended for low-risk patients who undergo transrectal

**Table 5.** AMP for prostate biopsy

Approach	Antimicrobials	Duration
Transperineal	Oral levofloxacin (500 mg)	Single dose
Trans-rectal		
Low risk	Oral levofloxacin (500 mg)+aminoglycosides	Single dose
High risk <sup>a)</sup>	Tazobactam/piperacillin (4.5 g)	Twice for one day

<sup>a)</sup>High risk: prostate volume  $\geq 75$  ml, diabetes, steroid dosing, immune-deficiency status, severe voiding disturbance (IPSS  $\geq 20$ ,  $Q_{max}$  of  $\leq 12$  ml/s, residual volume  $\geq 100$  ml).

prostate biopsy (EL; II, RG; B). Additionally, a combination of aminoglycosides with fluoroquinolones [42] or tazobactam/piperacillin [43] can reduce the rate of infection and is considered to be an optional selection (EL; IVa, RG; C1). Regarding AMP for high-risk patients, who have a large prostate volume of 75 ml or more, diabetes, steroid dosing, voiding dysfunction (IPSS  $\geq$ 20,  $Q_{\max}$   $\leq$ 12 ml/s, residual volume  $\geq$ 100 ml), or immune suppression status, tazobactam/piperacillin at 4.5 g twice a day is recommended (EL; III, RG; B) (Table 5) [44].

### 3. Intra-rectal Disinfection and Targeted AMP Using Povidone Iodine for Transrectal Prostate Biopsy

Intra-rectal disinfection using povidone iodine is recommended prior to a biopsy procedure. A retrospective study that was previously conducted in Japan showed that non-performance of intra-rectal disinfection was a significant risk factor for post-transrectal prostate biopsy infection (univariate analysis,  $p=0.0001$ ) (EL; II, RG; B) [34]. In addition, several studies have reported that targeted AMP is effective for reducing the rate of post-prostate biopsy infection. Therefore, a rectal swab culture in advance of a transrectal prostate biopsy is recommended, especially in high-risk patients, such as those with a history of previous treatment by antimicrobials (EL; II, RG; B) [45-47].

## CONCLUSIONS

Possible risk factors for SSIs include AMP methodology, as well as various patient-related and medical care-related factors. Wearing double gloves should be mandatory in all major surgical procedures, and a double glove indicator system should be the preferred option [48]. A previous report showed that surgical glove perforation significantly increases the risk of SSI when surgical AMP is not administered [49].

According to a previous report, a surgical safety checklist reduces morbidity and mortality in a global population. The rates of complications and death of inpatients declined with the introduction of the checklist; from 11.0% and 1.5% before the introduction to 7.0% and 0.8% after the introduction [50].

Therefore, appropriately selecting and administering antimicrobials in pre-surgical situations, as well as evaluating

and controlling the preoperative environment, which may affect the occurrence of SSI, are important.

## CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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