Clinical aspects of antimicrobial prophylaxis for invasive urological procedures

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The essential value of antimicrobial prophylaxis is to defend the patient undergoing invasive diagnostic procedures or surgery against infectious complications by reducing the bacterial load. *Escherichia coli* remains the predominant uropathogen (70–80%) isolated in acute community-acquired uncomplicated infections, followed by *Staphylococcus saprophyticus* (10 to 15%). *Klebsiella, Enterobacter*, *Proteus* species, and enterococci infrequently cause uncomplicated cystitis and pyelonephritis. The pathogens traditionally associated with UTI are altering many of their features, particularly because of antimicrobial resistance. Currently, only transurethral resection of prostate and prostate biopsy has been well studied and has high and moderately high levels of evidence in favor of using antibiotic prophylaxis. Other urological interventions have not been well studied. The moderate to low evidence suggests that there is no need for antibiotic prophylaxis in cystoscopy, urodynamic investigations, and extracorporeal shock-wave lithotripsy, whereas the low evidence favors the use of antibiotic prophylaxis for therapeutic ureterorenoscopy and percutaneous nephrolithotomy. The scarce data from studies on transurethral resection of bladder tumors cannot provide a definitive indication for antibiotic prophylaxis for this intervention.

Keywords: Urological surgery, Antibiotic prophylaxis, Drug resistance, Fosfomycin trometamol

Introduction

The use of antimicrobial prophylaxis in urology has been controversial for many years because most of the studies carried out have not been well designed and lack statistical significance, with many contradictions regarding the definition and evaluation of risk factors, as well as big discrepancies in treatment protocols and therapy choices in Europe. Given this situation, it is apparent that guidelines based on solid scientific evidence are badly needed in this area.

First of all, it is important to point out that antibiotic prophylaxis and antibiotic therapy are two different concepts. The purpose of antimicrobial prophylaxis is to prevent infection associated with diagnostic or therapeutic procedures. Antibiotic therapy instead is the treatment of a clinically suspected or microbiologically-demonstrated infection.

The main purpose of antimicrobial prophylaxis is to reduce the risk of infectious complications for patients undergoing diagnostic or invasive surgical procedures. The objectives of prophylaxis in urology are also much debated. There is without a doubt unanimity regarding the prevention of symptoms linked to infection such as fever, prostatitis, epididymitis and urosepsis. However, there are major doubts about trying to contain the appearance of asymptomatic bacteriuria or minor infections which generally occur subclinically and tend to resolve spontaneously.

Another important objective which is part of the debate is prevention of non-urological infections such as endocarditis or postoperative pneumonia which can occasionally follow urological procedures and operations.

Before beginning antibiotic prophylaxis, patients should be subdivided into different categories based on the following criteria:

- the patient's general condition according to criteria of the American Society of Anesthesiology (ASA);
- the presence of general risk factors: advanced age, diabetes mellitus, immunocompromised, malnutrition, important alterations in weight such as obesity or very underweight patients;
- the presence of specific exogenous or endogenous risk factors such as history of lower urinary tract infections, use of permanent urinary catheter, bacterial load, previous operations, genetic factors.[1]

The purpose of this literature review is to clarify the possible role of antibiotic prophylaxis in diagnostic urological procedures, and to investigate three principal aspects of this problem, including:

- which procedures require prophylaxis?
- which antibiotics are appropriate for prophylaxis?

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- what can be done to avoid the induction of bacterial antibiotic resistance?

Risk Factors

Risk factors are often underestimated in controlled clinical studies, but they are very important in the overall management of the patient and in selecting the proper pharmaceutical. As mentioned above, risk factors can be divided into three groups:

- the patient's general condition according to ASA criteria (score P1–P5);
- general risk factors such as advanced age, diabetes mellitus, immunocompromised, malnutrition, altered weight (obese or underweight);
- specific exogenous or endogenous risk factors such as previous history of urological infection, use of permanent urinary catheter, bacterial load, previous operations, genetic factors.

The European Association of Urology (EAU Expert Group) classifies endoscopic procedures carried out with transurethral access as 'clean-contaminated' since urinalysis does not always reveal the presence of bacteria and the lower urinary tract hosts resident microflora even in the presence of sterile urine.[2,3]

Principles of Antimicrobial Prophylaxis

The main objective of antimicrobial prophylaxis is to reduce the risk of infection, with a preventive rather than curative aim, and at the same time to marginalize the possible induction of resistant bacteria which often cause therapy failure. The literature data suggest that an intelligent use of antimicrobial prophylaxis can help reduce the enormous abuse of antibiotics as well as the unfavorable events arising from this.[3,4]

It is important that the choice of antibiotic to be used for prophylaxis take into account the patient's individual risk factors and that it be based on the results obtained from previous urinalyses. It also should be emphasized that antimicrobial prophylaxis should in no way be considered a substitute for standard hygiene and sanitary preventive measures.[5,6]

Timing

There is a precise window of time in which antimicrobial prophylaxis should be administered. The ideal period would be 1–2 hours prior to the procedure to be carried out, although some studies maintain that equally efficacious results can be obtained when administering the prophylaxis 3 hours after beginning the procedure.[7]

It is especially important that oral antibiotics be administered at least 1 hour prior to the procedure, whereas those administered intravenously may be given at the time of induction of anesthesia, so as to provide optimum concentrations of the active ingredient during the period of highest infectious risk.

Administration route

It has been shown that antibiotics which possess adequate bioavailability can be administered either orally or intravenously, with equal efficacy. For this reason, it is recommended to use oral administration for all procedures where the patient can easily take the drug one hour before the intervention. For all other cases, intravenous administration is recommended.

Treatment duration

There are no precise indications for the duration of antibiotic prophylaxis administration but in general this should be reduced to the minimum. In theory, a single dose should be adequate if given prior to the procedure, and this should be repeated only if important risk factors are present which might induce the physician to prolong drug administration.

Antibiotic selection

There are no clear indications at the moment in Europe in regard to choice of antibiotic for prophylaxis, given the considerable variety of drugs used, their spectra and antibacterial power. There is more bacterial resistance in southern Europe compared to northern Europe, correlated with four times the number of sales of antimicrobial agents in Mediterranean countries.[8]

Therefore, it is necessary to be knowledgeable about the profile of local pathogens, their susceptibility and virulence, in order to establish local guidelines regarding drug choice. It is also essential to define the principal pathogens involved with various diagnostic and therapeutic procedures. Antibiotic choice must also be based on considerations of specific risk factors for each treatment, the bacterial load, the target organ and role of local inflammation. It is recommended to use broad-spectrum antibiotics such as the fluoroquinolones and vancomycin as little as possible and to reserve their use for eventual treatment.

Urinary tract infection pathogens

The etiology of urinary tract infections (UTIs) has been well established for many years and is therefore not of much interest. *Escherichia coli* has been considered the primary uropathogen, although today, thanks to progress made in molecular microbiology, other microorganisms are being isolated with increasing frequency. In addition, the common pathogens associated with UTIs have been mutating and becoming more resistant, thus being an important cause of therapy failure.

Therefore, in coming years antimicrobial prophylaxis must be adapted to this bacterial evolution, through various changes, with the goal of limiting the outbreak and reducing the propagation of resistant bacteria.

UTIs are also the result of factors linked with the patient such as age, diabetes, spinal cord marrow lesions, catheterization, etc. UTIs should be considered the result of complex and multifactoral processes in which a group of causes interacts in bringing about

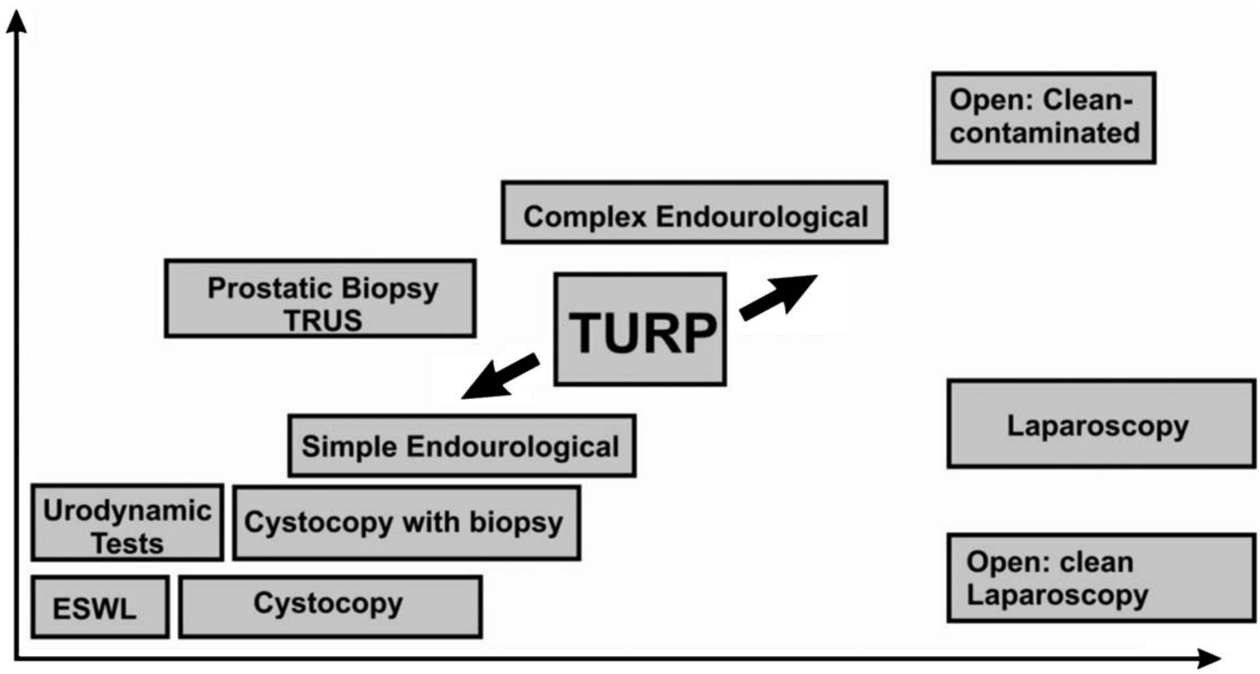

Figure 1 Urological procedures.[10]

the infection. It is therefore not difficult to understand why a common pathogen does not cause any symptoms in a healthy individual but can instead provoke a serious disease in patients presenting with various risk factors and who are therefore more susceptible to infectious events.

Most uncomplicated UTIs in the USA are caused by *E. coli* (80%) or *Staphylococcus saprophyticus* (10–15%). *Klebsiella, Enterobacter, Proteus* and enterococci are more rarely responsible for uncomplicated UTIs such as cystitis or pyelonephritis. The mycetes, especially *Candida albicans* and other *Candida* species, determine more than 10% of positive urinalyses carried out in patients treated in specialized clinics and often cause complicated UTIs.[9]

Procedures

Figure 1 illustrates the urological procedures which will be discussed in the following sessions.

The Working Group EAU/ESIU (European Association of Urology, section 'Infections in Urology') suggested the diagnostic and therapeutic urological procedures based on their ability to contaminate or cause infection (adapted from EAU Guidelines, 2013).[10]

Cystoscopy

Cystoscopy is a widely used diagnostic procedure in urology. It is carried out using a cystoscope (endoscope) which can be:

- standard (rigid);
- flexible.

The type of cystoscope used depends on the purpose of the examination, without prejudicing in any way the objectivity of the investigation. The procedure takes about 5–20 minutes. Before introducing the cystoscope into the urethra it is necessary to apply a local anesthetic cream in the urethra and then proceed with introducing the cystoscope into the bladder through the urethra. During the procedure it is possible, by using water or saline solution introduced through the cystoscope, to enlarge the bladder so as to facilitate vision of the bladder mucosa. If anomalous lesions are located during the procedure, it is possible to make a biopsy that then can be analyzed pathologically.

Risk of infection

In an early study Clark and Higgs[11] investigated the presence of asymptomatic bacteriuria (BAS) three days after cystoscopy and found it to be present in 12/161 patients (7.5%).

Cruz *et al.*[12] published a randomized controlled study (RCT) in 1993 involving 2172 patients (1057 controlled and 1115 'treated') and all had pre-cystoscopy sterile urine. Patients were evaluated on the basis of the presence of BAS and symptomatic UTI 2–3 days and one month after cystoscopy. The treated group was administered a single 1-g dose of ceftriaxone i.m. The incidence of BAS in the untreated group was 3.02 versus 1.52% in the treated group (not statistically significant); symptomatic UTI was 10.2% in the untreated group versus 2.5% in the treated group and this was statistically significantly different.

Wilson *et al.*[13] reported the results of an RCT involving 234 patients (122 controls/112 treated), demonstrating no significant difference in preventing BAS and symptomatic UTI in either group. Two other studies found spontaneous bacteriuria occurring in 2.7%[14] and in 4.5%[15] of the study populations. These found no specific causes of spontaneous contamination and also that spontaneous cure of the bacteriuria was high.

Johnson *et al.*[16] published a study on flexible cystoscopy where they administered a single dose of trimethroprim or ciprofloxacin to their patients, obtaining more than a 50% reduction in post-cystoscopic bacteriuria compared to placebo (2, 3.2 and 6.8% respectively). These results confirm those of Cruz *et al.*[12]

There are case histories describing the incidence of post-cystoscopy infections in patients not administered antimicrobial prophylaxis. For example, Almallah *et al.*[14] reported a BAS of 4.9% in 103 patients 48 hours after cystoscopy. While 14% of patients reported having irritating symptoms 48 hours following cystoscopy, only a small percentage had bacteriuria, equal to the 1.9% incidence of symptomatic UTI.

Clark and Higgs[11] found an incidence of 7.5% BAS following cystoscopy. These percentages are even lower when considering only patients without risk factors, in which case the incidence drops to 0.8%.

In conclusion, after cytoscopy, the incidence of BAS and other infections with clinical implications is low, and antimicrobial prophylaxis plays a marginal role in decreasing their incidence. Not all patients require antimicrobial prophylaxis but only those with well identified risk factors. If all patients were given antibiotic prophylaxis for this procedure, it would be a huge, overall consumption of antibiotics, given the frequency with which cystoscopy is performed.

Urodynamic Testing

Urodynamic tests are procedures designed to evaluate the efficiency of the bladder, of the sphincters and urethra in containing and releasing urine. The most frequent urodynamic test is intended to evaluate the contractile and retentive functions of the bladder (i.e. the detrusor muscle of the urinary bladder); it allows registration of involuntary contractions of the bladder which are responsible for urinary incontinence. Therefore this test is indicated for recognizing the cause and nature of disturbances of the lower urinary tract.

These procedures can be very complex, ranging from simple observations to precise measurements using sophisticated equipment. The most accurate measurements involve use of imaging instruments showing images of filling and emptying of the bladder, or use of pressure sensors which register the internal pressure of the bladder and abdominal torque together with muscular and nervous activity.

Most urodynamic tests do not require specific preparation, but can involve changes in liquid consumption or suspension of certain specific drugs on the part of the patient, and it may be essential that the patient have a full bladder at the time of the test.

Urodynamic tests include the following:

- uroflometry;
- measurement of post-micturition residue;
- cystometry;
- study of flow pressure;
- measurement of leak point pressure;
- electromyography;
- urodynamic video tests.

The invasiveness of urodynamic tests is limited to an invasion of the 'patient's private intimacy', but these are otherwise not considered as contaminated procedures.

Risk of infection

The case reports present in the literature report pre-urodynamic test urinalysis bacteriuria as being between 1.9 and 10.3%.[17–20] In patients who are not administered antimicrobial prophylaxis, post-urodynamic bacteriuria ranges between 1.1 and 19.6%, two to three days afterwards and 4.1 to 13.9% after a week of follow-up.[17,18,20–25] In those patients who are given antibiotic prophylaxis, the incidence of bacteriuria is between 1.8 and 4.0% in women and between 3.6 and 6.2% in men.[26] Some studies indicate that advanced age is a risk factor for the increased incidence of post-urodynamic bacteriuria.

Latthe *et al.*[27] reported data on 995 patients in a meta-analysis which considered eight RCTs, demonstrating that bacteriuria (defined as $>10^5$ colony forming units [CFU]/ml) was reduced by 40% by antibiotic prophylaxis. These researchers calculated that to avoid one single episode of bacteriuria it would be necessary to treat at least 13 patients with antibiotic prophylaxis.

Cundiff *et al.*[28] investigated the role of prophylaxis in a single day in women who underwent urodynamic tests or cystoscopy. They found no significant difference between those patients given antimicrobial prophylaxis and those who were not.

Logadottir *et al.*[24] studied the infection risk in men who underwent invasive urodynamic tests and found that 4.1% suffered bacteriuria and 2.5% fever.

On the basis of this evidence, one can conclude, as we did with cystoscopy, that the low frequency of infectious events following urodynamic tests means that antimicrobial prophylaxis plays a marginal role in decreasing their incidence. Not all patients require antimicrobial prophylaxis but only those with well identified risk factors. It should be emphasized that the true role of antimicrobial prophylaxis in patients without risk factors requires more study.

Prostatic Biopsy

Prostatic biopsy is a technique designed to remove tissue fragments or cells from the prostate for microscopic examination. In this procedure, prostatic tissue samples are taken using a specific biopsy needle in order to determine whether there are atypical or carcinogenic cells present. The biopsy is the only method capable of confirming the diagnosis of prostate cancer.

Prostatic biopsy can be carried out with two different methods:

- transrectally, which is the most commonly performed;
- perineally, through the space between the scrotum and rectum.

Patients usually lie in the left lateral decubitus position with knees and hips flexed 90 degrees. An arm board attached parallel to the table and a pillow between the knees helps maintain this position. The buttocks should be flush with the end of the table to permit the physician to manipulate the ultrasound probe and bioptic gun without impediment. If necessary, the right lateral decubitus or lithotomy position can be used.

During the procedure, the prostatic volume is evaluated; ultrasound images are acquired on the transversal rather than sagittal plane. Generally, evaluation of the prostate is made starting from the base of the gland and proceeding toward the apex. The most frequently used equipment for prostatic biopsy is a caliber 18 bioptic gun, an instrument furnished with a needle that uses a spring system to work and which can be introduced while using the ultrasound as a guide. Most ultrasound examinations provide better route determination of the bioptic needle on the sagittal plane. The bioptic gun advances the 0.5 cm needle and extracts samples for the next 1.5 cm of tissue with an extended point of 0.5 cm beyond the sampled area. When the peripheral area is sampled, the point of the needle can be positioned 0.5 cm posteriorly to the prostatic capsule before advancing. If the needle is advanced excessively through the capsule, it can collect tissue sample which is located too anteriorly, losing the parts of the organ which are most commonly the site of tumor. By pushing the ultrasound probe against the rectum, the discomfort of the bioptic needle going through rectal mucosa is minimized, just as rubbing the skin reduces the discomfort after an injection. Bioptic samples are usually stored in 10% formaldehyde solution. They must be inserted in different containers for tissues coming from the right or left sides of the prostate gland.[29]

Risk of infection

The frequency of infectious complications for prostatic biopsy in some studies carried out in the 1990s is over 48%.[30,31] More recent cohort studies report incidences of infectious complications such as febrile UTI, acute prostatitis and sepsis as between 2.9 and 10%.[32–34] In RCT, patients who were not administered antimicrobial prophylaxis experienced an incidence of bacteriuria between 5 and 26%, and a frequency of more than 10% of febrile UTI.[35–37] Both the bacteriuria and febrile UTI were significantly reduced by antimicrobial prophylaxis, with studies reporting an incidence of less than 5% in low-risk patients.[30,31,35–37] A single day of prophylaxis, and even a single dose of antibiotic[37–41] can be useful in reducing infectious complications to 1% or even less, with an incidence of sepsis of less than 0.5%. Some studies of cohorts on antimicrobial prophylaxis have confirmed this low incidence of infection.[42,43]

Lindstedt *et al.*[40] have studied the most correct administration time, reporting that the antibiotic may be administered contemporaneously with the procedure, especially if given intravenously, or also 1 to 2 hours before the biopsy.

Transurethral Resection of Bladder Tumor (TURB)

Resection of bladder tumors is one of the most frequently performed urological procedures. It takes between 10 to 60 minutes to carry out, depending on the number, dimension and invasiveness of the tumors. TURB, carried out under local or general anesthesia, is the first treatment for visible lesions and is performed to remove all visible tumors and to obtain histological fragments in order to determine the staging and grade of the cancer. With the aim of creating a complete anatomical picture of the bladder and precise localization of the tumor lesions, it is useful to first carry out endoscopy with a 70° lens or flexible cystoscope.

The resection should instead be performed with a 30° lens placed in a resectoscope sheath which allows better visualization of the cutting loop. A video terminal during the endoscopy provides several advantages: amplification and conservation of images of the entire procedure but especially, it permits the surgeon to carry out the operation using the video screen rather than the instrument's optic, reducing the risk of coming into contact with fluids produced during the procedure. The resection is carried out piecemeal, avoiding a clean cut. The easily extracted tumors, of low grade, can often be removed without use of a resector, only using electrofulguration, thereby reducing the possibility of perforating the bladder wall. High grade, more solid or flat tumors require use of the electrode. After total resection of the tumor it is necessary to carry out careful cauterization. Lifting the tumor edge away from the detrusor lessens the chance of perforation. After all visible tumor is resected, an additional pass of the cutting loop or a cold cup biopsy can be obtained to send to pathology separately to determine the presence of tumor invasion of the muscle. It is very useful to do a final check of the bladder to control hemostasis after removal of bladder tissue.

TURB is usually carried out using sterile water without electrolytes since saline solutions conduct electricity and disperse the energy of the monopolar cautery cutting loop. Use of general anesthesia with muscle relaxants prevents the detrusor reflex during resection. Resection of diverticular tumors has a high risk of perforation of the bladder wall and in these cases it is also very difficult to stage the tumor because the underlying detrusor muscle is absent. Invasion of the lamina propria immediately involves perivesical fat or stage T3a. Low-grade diverticular tumors are best treated with a combination of resection and fulguration of the base. Conservative resection can be followed with subsequent repeated resection if the final pathologic interpretation is high grade. High-grade tumors require adequate sampling of the tumor base through biopsy, often including perivesical fat, despite the near certainty of bladder perforation. Anterior wall tumors or those localized at the dome in patients with large bladders can be difficult to reach. Care must be taken during resection near the ureteral orifice to prevent obstruction from scarring after fulguration.

Resection of the intramural ureter can lead to complete eradication of the tumor but risks reflux of malignant cells towards the upper urinary tract. The clinical implications of this reflux are not clear. Alternatively, small tumors maybe resected using cold cup biopsy forceps alone. This is especially helpful for the thin-walled bladder of elderly women, who are predisposed to perforation. If perforation occurs, the cup causes a smaller hole than does the cutting loop.

If a tumor appears to be muscle-invasive, biopsies of the borders and base to establish level of invasion may be performed in lieu of complete resection, since cystectomy will likely follow confirmatory biopsies. Failure to demonstrate invasion necessitates a repeated resection unless the decision is made to proceed to cystectomy based on factors other than muscle invasion.[29]

Risk of infection

Unfortunately there are only a few studies in the literature, with weak evidence and small samples, which have evaluated antibiotic prophylaxis for TURB.[44–46] The results of these studies do not support the use of antimicrobial prophylaxis for TURB. The two studies by Delavierre[46] and MacDermott[44] are out of date and have small study populations. Both studies report reduced bacteriuria following TURB in those patients administered antibiotic prophylaxis, but the reductions were not statistically significant. Furthermore, Delavierre's study shows no difference in the occurrence of UTI post-TURB between the group given antibiotic prophylaxis and the placebo group, with an incidence of 0% in both. It must be emphasized, however, that the studies were carried out only on resection of very small tumors, or on electrofulguration, which are interventions similar to simple cystoscopy in terms of level of contamination, and therefore do not represent the range of bladder tumor resections which can be small, single papillary tumors (Ta, G1–2) or large, muscle-invading tumors (T2, G3), or even the not unusual situation of resection of multiple papillary tumors. There is a definite need for more studies which investigate the whole range of TURB operations, to clarify the differences among them in terms of invasiveness, difficulty, duration and other risk factors.

Transurethral Resection of the Prostate (TURP)

TURP is a surgical procedure which is designed to remove all or part of the prostate, when the gland is enlarged. The operation lasts about one hour and is usually carried out with the patient being administered epidural anesthesia. Traditionally, TURP has been performed using monopolar technology with 1.5% glycine or mannitol as nonhemolytic fluids for irrigation. This technique has been used for a very long time with considerable success, but concerns about TURP syndrome (due to reabsorption of lavage fluids which causes confusion, nausea, vomiting, nervous disturbances and circulatory instability) have led to the introduction of bipolar TURP. Recently, standard monopolar TURP is now being challenged by the use of bipolar resection, the rationale being to reduce the complications of standard monopolar TURP, thereby improving the quality of the operation from the point of view of both the surgeon and the patient. In addition to monopolar or bipolar surgical techniques, there are other methods of removing prostatic adenomas. Every surgical technique employs the principle that the resection should be performed in a routine step-by-step manner.[29] The most commonly used are listed below.

- Transurethral incision of the prostate. This procedure is similar to TURP, but involves making one or two small cuts in the neck of the bladder and prostate rather than removing part of the prostate. It is usually only suitable for men whose prostate is only moderately enlarged.
- Open prostatectomy. This is not a common procedure and is usually only carried out if the patient has a very large, benign prostate.
- Minimally invasive treatment (holmium/thulium laser electrovaporization or enucleation of the

prostate). In these procedures, laser or electrical energy is used to burn off excess tissue from the prostate. Generally these procedures are the least invasive but do not remove as much tissue as standard or bipolar TURP.

- Transurethral needle ablation of the prostate. This procedure uses needles to deliver heat to the prostatic tissue. This procedure may have fewer complications than TURP, but the possibility of needing a repeat procedure is higher.

Risk of infection

TURP should not be considered a diagnostic maneuver but rather a true surgical procedure which has an impact on daily clinico-surgical practice, being one of the most commonly performed endourological procedures. TURP is the most thoroughly studied urological procedure in terms of use of antimicrobial prophylaxis. There are more than 50 quality studies published in the literature. After undergoing TURP, more than 70% of patients experience bacteriuria.

Grabe[47] analyzed the literature between 1980 and 1987 in a review article, showing that antimicrobial prophylaxis can reduce postoperative bacteriuria from 34 to 10% in patients who had a preoperative negative urinalysis.

Berry and Barratt[48] published a high-quality meta-analysis in 2002, analyzing 32 randomized controlled trials. The authors conclude that antibiotic prophylaxis reduces the risk of postoperative bacteriuria from 26 to 9%. In 2005, Qiang *et al.*[49] reported similar conclusions in a systematic review of the literature.

When considering the appearance of sepsis, instead, Berry and Barrat[48] reported an even more significant result, showing that antibiotic prophylaxis reduces this complication from 4.4% to less than 1% of cases. Both these articles show that short term prophylaxis (<72 h) is more efficacious than a single dose, but less efficacious than treatment given for a week.

Wagenlehner *et al.*[3] confirmed the above results in a multicenter RCT but observed less of a difference between patients treated with antimicrobial prophylaxis and those given a placebo.

In conclusion, there is important evidence from high quality studies indicating that antibiotic prophylaxis for TURP reduces the incidence of febrile infections, sepsis and postoperative bacteriuria.

Extracorporeal Shockwave Lithotripsy (ESWL)

Before the introduction of ESWL in 1980, the only available treatment for calculi that could not pass through the urinary tract was open surgery. Since then, ESWL has become the preferred tool in the urologist's armamentarium for the treatment of renal stones, proximal stones, and midureteral stones. Compared with open and endoscopic procedures, ESWL is minimally invasive, exposes patients to less anesthesia, and yields equivalent stone-free rates in appropriately selected patients.

The efficacy of ESWL lies in its ability to pulverize calculi into smaller fragments *in vivo*, which the body can then expulse spontaneously. Shockwaves are generated and then focused onto a point within the body. The shockwaves propagate through the body with negligible dissipation of energy (and therefore damage) owing to the minimal difference in density of the soft tissues. At the stone-fluid interface, the relatively large difference in density, coupled with the concentration of multiple shockwaves in a small area, produces a large dissipation of energy. Via various mechanisms, this energy is then able to overcome the tensile strength of the calculi, leading to fragmentation. Repetition of this process eventually leads to pulverization of the calculi into small fragments (ideally <1 mm) that the body can pass spontaneously and painlessly.

All lithotripsy instruments share four basic components: (1) a shockwave generator, (2) a focusing system, (3) a coupling mechanism, and (4) an imaging/localization unit.

Shockwaves can be generated in 1 of 3 ways, as follows:

- electrohydraulic: The original method of shockwave generation (used in the Dornier HM3) was electrohydraulic, meaning that the shockwave is produced via spark-gap technology. In an electrohydraulic generator, a high-voltage electrical current passes across a spark-gap electrode located within a water-filled container. The discharge of energy produces a vaporization bubble, which expands and immediately collapses, thus generating a high-energy pressure wave.
- piezoelectric: The piezoelectric effect produces electricity via application of mechanical stress. The Curies first demonstrated this in 1880. The following year, Gabriel Lippman theorized the reversibility of this effect, which was later confirmed by the Curies. The piezoelectric generator takes advantage of this effect. Piezoelectric ceramics or crystals, set in a water-filled container, are stimulated via high-frequency electrical pulses. The alternating stress/strain changes in the material create ultrasonic vibrations, resulting in the production of a shockwave.
- electromagnetic: In an electromagnetic generator, high voltage is applied to an electromagnetic coil, similar to the effect in a stereo loudspeaker. This coil, either directly or via a secondary coil, induces high-frequency vibration in an adjacent metallic membrane. This vibration is then transferred to a wave-propagating medium (i.e. water) to produce shockwaves. A stone is fragmented when the force of the shockwaves overcomes the tensile strength of

the stone. Although not completely understood, fragmentation is thought to occur through a combination of methods, including compressive and tensile forces, erosion, shearing, spalling, and cavitation. Of these various forces, the generation of compressive and tensile forces and cavitation are thought to be the most important. When a shockwave is propagated through a medium (water), it loses very little energy until it crosses into a medium with a different density. If the medium is denser, compressive forces are produced in the new medium. Similarly, if the new medium is less dense, tensile stress is produced on the first medium. Upon hitting the anterior surface of a stone, the change in density creates compressive forces, causing fragmentation. As the wave proceeds through the stone to the posterior surface, the change from high to low density reflects part of the shockwave's energy, producing tensile forces, which again disrupt and fragment the stone. In cavitation, shockwave energy applied at a focal point leads to vaporization of the liquid with generation of water–vapor bubbles. These gaseous bubbles collapse explosively, creating microjets that fracture and erode the calculus. This process can be monitored with real-time ultrasonography during the treatment and appears as swirling fragments and liquid in the focal zone.[50]

Risk of infection

Although ESWL is one of the most frequently employed procedures in urology, there are few reports in the literature regarding the utility of antimicrobial prophylaxis. Some studies have analyzed the follow-up in patients without risk factors, showing that bacteriuria occurs in fewer than 5% of these patients.[51–53] Most studies have low numbers of patients as well as low incidence of infection, so it is difficult to draw complete conclusions. Given these drawbacks, the meta-analysis of Pearle and Roehrborn[54] confirmed that antibiotic prophylaxis in patients with sterile, pre-ESWL urine is useful and reduces the incidence of post-ESWL complications. The frequency of bacteriuria and/or symptomatic UTI is between 0 and 28% in untreated groups and between 0 and 7% in those patients given prophylaxis. The authors calculated that the relative risk of contracting a UTI in untreated patients is 5.7% and in treated 2.1%. However, these results are not confirmed in any other study we evaluated.[55–58] The presence of a struvite stone was identified as a risk factor for developing post-ESWL bacteriuria.[53]

We can conclude that in patients with sterile urine, without risk factors and with uncomplicated stones (both kidney and ureteral), there is a low risk of post-ESWL bacteriuria/UTI, a limited reduction of risk by antibiotic prophylaxis, and therefore no evidence for administering antibiotic prophylaxis in low-risk patients, which represents the greater percentage of patients treated with ESWL. Antimicrobial prophylaxis could be considered for patients with complicated or staghorn calculi.

Ureteroscopy (URS)

Ureteroscopy is defined as upper urinary tract endoscopy performed most commonly with an endoscope passed through the urethra, bladder, and then directly into the upper urinary tract. Indications for ureteroscopy have broadened from diagnostic endoscopy to various minimally invasive therapies. Endoscopic lithotripsy, treatment of upper urinary tract urothelial malignancies, stricture incisions, and ureteropelvic junction obstruction repair are all current treatments facilitated by contemporary ureteroscopic techniques. Because the application of ureteroscopic procedures has evolved from a diagnostic tool to a facilitator in complex therapeutic interventions, a proportional increase in the rate and severity of complications would be expected.

This endoscopic procedure is performed with the goal of inflicting the least possible trauma on the upper urinary tract. Ureteroscopic access is obtained with a wireless ureteroscopy technique, if possible. The ureteral orifice is visualized and intubated without the assistance of a guidewire. The ureter is traversed with a no-touch technique, and the ureter and renal collecting system are mapped. In a recent prospective study of 460 consecutive upper-tract endoscopies, no-touch ureteroscopy was successfully performed in most patients without prior stenting (24%) or ureteral dilation (11%).[59] This wireless form of flexible ureteroscopy eliminates the potential trauma, mucosal irritation, and inadvertent manipulation of stones or tumors caused by guidewires. The flexible ureteroscope is passed from calyx to calyx, and, frequently, diluted contrast fluid is injected through the working channel of the endoscope to help ensure the entire collecting system is inspected. This approach is particularly helpful when the collecting system is evaluated for mucosal lesions of the excretory channels. Abundant fluid irrigation is necessary for passage of a rigid ureteroscope and to allow endoscopic visualization.

Therapeutic ureteroscopy is used in diverse applications, including in the treatment of stones, urothelial tumors, and stenosis or stricture disease. Ureteroscopy is a safe and minimally invasive method of treating stone disease in the kidneys and ureter. It can be used either as primary therapy or as salvage therapy for residual stones following treatment with other modalities such as extracorporeal shock-wave lithotripsy (ESWL). Compared with ESWL, ureteroscopic removal of stones achieves a greater stone-free state, but leads to more complications and longer hospital stays.[60] Furthermore, in select cases, ureteroscopy has been shown to be a viable and effective means of treating stone disease in pregnant women and in pediatric patients.

Ureteroscopy has also become a powerful tool in the treatment and surveillance of transitional cell tumors of the upper tracts, especially bilateral disease processes and tumors in solitary kidneys.[61,62] In addition, ureteroscopy can be used to treat stenosis that develops following ureteral reimplantation and to treat ureteropelvic junction stenosis. In each case, an energy source is delivered through the working channel of the endoscope to fragment, ablate, and/or incise the lesion. Additional accessories can also be passed to remove stone fragments or to obtain biopsy samples.

Risk of infection

There are no studies in the literature regarding the role of antibiotic prophylaxis for diagnostic ureteroscopy – only for therapeutic ureteroscopy, and in particular studies evaluating prophylaxis for management of calculi with ureteroscopy.[63,64] Two studies indicate reduced bacteria, although not UTI when antimicrobial prophylaxis is administered.[63,64]

Hendrikx *et al.*[65] compared ESWL and ureteroscopy for treatment of calculi in different sites (mid and distal ureteral stones), finding more complications, including infection, in patients treated with ureteroscopy than those treated with ESWL. These studies are biased because they do not differentiate between degree of invasiveness of a procedure, between various types of calculi in terms of their dimension and site (impacted proximal stone versus small mid and lower stones), between complexity of the surgery, duration of the operation, experience of the surgeon – all of which are important factors affecting the risk of infection of the procedure.[66]

It can be concluded that there is no conclusive scientific evidence that supports the use of antibiotic prophylaxis in diagnostic ureteroscopy, while there is low to moderate evidence supporting its use for therapeutic ureteroscopy. Studies which investigate the use of prophylaxis for various procedures based on risk factors which complicate their outcome are particularly needed.

Percutaneous Nephrolithotomy (PCNL)

Management of nephrolithiasis through percutaneous techniques is most often reserved for stones greater than 1.5 cm to 2.0 cm, in a staghorn configuration, behind a stenosed infundibulum, in a calyceal diverticulum, in a kidney with ureteropelvic junction obstruction, or in anomalous kidneys. Stone-free rates for non-staghorn renal stones approach 95% with PCNL as compared to 85% with ureteroscopy and 75% with ESWL. For staghorn renal calculi, stone-free rates reach 78% with PCNL and 54% with ureteroscopy. PCNL has largely replaced open and laparoscopic surgery in the management of complex and large renal stones. Compared to open surgery, PCNL allows patients quicker convalescence, less morbidity, and decreased cost. Many times, the patient arrives in the operating room with percutaneous access (generally a small nephroureteral catheter placed by interventional radiology that affords entry access to the ureter through the desired calyx). Some urologists carry out percutaneous access themselves at the time of the procedure. Positioning is one of the most critical aspects of the procedure. Under fluoroscopic guidance, a wire is passed into the percutaneous nephroureteral access catheter, down the ureter and into the bladder. The access catheter is removed, leaving only the guidewire. The next step is to dilate the fascia so the nephroscopic sheath can be placed at the level of the calices and pelvis (collecting system). The rigid dilators create a working access canal by sequentially upsizing the dilators over the working wire. Once the 30-French dilator is inserted, the working sheath is placed over the dilator into the collecting system. In current practice, rigid dilators have largely been replaced by high-pressure nephrostomy tract balloon dilators. At this point, a nephrostogram should be done to confirm placement of access sheath. Then the nephroscope is introduced into the sheath to visually examine the collecting system. The stone burden is identified and evaluated and the stones are then fragmented as necessary and removed from the collecting system. There are a variety of instruments used for removing stones. These include tricep forceps, alligator forceps, and stone baskets. Generally the stone is too large to simply remove through the access sheath and fragmentation is necessary.

Several types of lithotripters are commonly utilized. A pneumatic lithotripter uses mechanical force to break up the stone by acting like a small jackhammer. An ultrasonic lithotripter uses ultrasound waves to fragment calculi. Modern devices often couple a suction port with the device to keep the stone in close proximity to probe and to remove pulverized fragments. Once the stones have been fragmented, the residual stone debris should be removed. Thorough visual and fluoroscopic inspection must be used to insure stone-free status. Once the stone burden is treated, generally a nephrostomy tube is placed into the collecting system either via the access sheath or over the safety wire. Contrast fluid is injected and its position is confirmed fluoroscopically.[29]

Risk of infection

PCNL plays a role analogous to that of therapeutic ureteroscopy, and shares the same risk factors for infectious complications. Charton *et al.*,[67] in a study

Table 1 Recommendations for perioperative urological antibiotic prophylaxis (EAU)[10]

Procedure	Pathogen	Prophylaxis	Antibiotics	Comments
Diagnostic procedures				
Transrectal biopsy of the prostate	Enterobacteriaceae	All patients	Fluoroquinolones	Single dose efficacious in low-risk patients
	Anaerobes?*		Trimethoprim± sulfamethoxazole (TMP±SMX) Metronidazole?*	Consider prolonging therapy in high-risk patients
Cystoscopy Urodynamic tests	Enterobacteriaceae Enterococci Staphylococci	No	TMP±SMX II Generation cephalosporins	Consider in high-risk patients
Ureteroscopy	Enterobacteriaceae Enterococci Staphylococci	No	TMP±SMX II generation cephalosporins	Consider in high-risk patients
Surgical, endoscopic procedures, lithotripsy (SWL)				
Shockwave lithotripsy (SWL)	Enterobacteriaceae Enterococci	No	TMP±SMX II and III generation cephalosporins Aminopenicillin/beta-lactamase inhibitor	
SWL with stent or nephrostomy tube	Enterobacteriaceae Enterococci	All patients	TMP±SMX II and III generation cephalosporins Aminopenicillin/beta-lactamase inhibitor	Patients at risk
Ureteroscopy for uncomplicated distal calculi	Enterobacteriaceae Enterococci Staphylococci	No	TMP±SMX II and III generation cephalosporins Aminopenicillin/beta-lactamase inhibitor Floroquinolones	Consider in patients at risk
Ureteroscopy of proximal or impacted stone or percutaneous stone extraction	Enterobacteriaceae Enterococci Staphylococci	All patients	TMP±SMX II and III generation cephalosporins Aminopenicillin/beta-lactamase inhibitor Floroquinolones	Short course Length to be determined Intravenous administration recommended at operation
Transurethral prostatectomy (TURP)	Enterobacteriaceae Enterococci	All patients	TMP±SMX II and III generation cephalosporins Aminopenicillin/beta-lactamase inhibitor	Low-risk patients with small prostate probably do not need prophylaxis
Transurethral resection of bladder tumor (TURB)	Enterobacteriaceae Enterococci	No	TMP±SMX II and III generation cephalosporins Aminopenicillin/beta-lactamase inhibitor	Consider in high-risk patients and large tumors

Note: TMP±SMX=Cotrimoxazole. *literature data uncertain.

evaluating a series of cases, found that bacteriuria occurred in 35% of cases and fever without bacteremia in 10% of patients post-P(C)NL who had not been administered antibiotic prophylaxis. The same authors showed that postoperative antibiotic treatment was necessary in 32% of patients due to an increase in transitory fever, whereas 3.5% experienced sepsis requiring antibiotic therapy.[67] In another study, Osman *et al*.[68] found post-P(C)NL transitory fever in 27.6% of patients and symptomatic UTI in 3.5% of patients who were not given antibiotics. Fourcade,[63] in a RCT, compared patients who were administered antibiotic prophylaxis with those untreated. Dogan *et al*.[69] compared two different prophylaxis approaches. Both these studies indicate that there is an evident decrease in infectious complications in patients given prophylaxis, independently of the choice of antibiotic.

In summary, we can affirm that there are still not enough data regarding the use of antibiotic prophylaxis in PCNL, but given the high incidence of infection reported in the literature and the presence of septic complications, proper antimicrobial prophylaxis could play a valuable role.

What Kind of Antibiotic Should Be Used for Prophylaxis in Urological Procedures?

The European Association of Urology (EAU)[10] provides precise indications on which antibiotics are appropriate for antimicrobial prophylaxis in diagnostic and endoscopic urological procedures (Table 1).

These Guidelines are not updated and cannot be applied to all countries in the European Union. Although it might be possible to create a universal model for performing diagnostic and surgical techniques which would apply to every country, this is not possible for antibiotic prophylaxis, where knowledge of the local epidemiology of resistant bacteria and the most common pathogens responsible for urological infections is mandatory.

The phenomenon of bacterial resistance can be underestimated when selecting an antibiotic for prophylaxis for instrumental or endoscopic interventions. Although *Escherichia coli* is still today the most responsible infectious pathogen of the urogenital tract which is capable of developing resistance to antibiotics, it is capable of producing beta-lactamases which hydrolyze the beta-lactam ring of beta-lactam antimicrobials, making them incapable of binding to the proper penicillin-binding protein targets. Resistance to broad-spectrum penicillins, such as ampicillin or amoxicillin, is usually conferred by plasmid coded beta-lactamases while resistance to third-generation cephalosporins is mostly conferred by extended spectrum beta-lactamases. An important threat that will require close surveillance in the future is the emergence of carbapenem resistance in *E. coli*. Resistance to fluoroquinolones has also increased extensively in recent years, reaching alarming levels, just as resistance to aminoglycoside antibiotics also needs to be taken into consideration.[70]

Another aspect of fundamental importance when evaluating the danger of antibiotic resistance is that of the enormous differences in relation to geographic areas. The annual report of the European Center of Disease Control or 2011 clearly shows the great differences in bacterial resistance to antibiotics in northern Europe, where resistance is decidedly lower than in some southern European countries which register alarming levels. This type of analysis should be carried out for each individual country, evaluating the current geographic distribution of bacterial resistance to antibiotics, so as to map resistance for individual healthcare clinics and hospitals.

On this basis, we should ask ourselves how we can truly create guidelines appropriate for all of Europe with only one treatment protocol, without taking into consideration data from each individual country, or even better, each individual hospital. Therefore, it is natural to hypothesize that national guidelines, from which can be derived geographic guidelines, which take into consideration zones of bacterial resistance when selecting a correct antibiotic for the prophylaxis of diagnostic and uroendoscopic procedures, would be very useful.

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