

Risk factors and predisposing conditions for urinary tract infection

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Abstract: Understanding individual and population-specific risk factors associated with recurrent urinary tract infections (UTIs) can help physicians tailor prophylactic strategies. Frequent intercourse, vulvovaginal atrophy, change of the local bacterial flora, history of UTIs during premenopause or in childhood, family history, and a nonsecretor blood type are substantiated risk factors for recurrent uncomplicated UTIs. This is a narrative review based on relevant literature according to the experience and expertise of the authors. Asymptomatic bacteriuria is generally benign; however, during pregnancy it is more common and is associated with an increased likelihood of symptomatic infection, which may harm the mother or fetus. Screening of pregnant women and appropriate treatment with antimicrobials must be balanced with the potential for adverse treatment-related outcomes; appropriate prophylaxis should be considered where possible. High-quality data are currently lacking on risks related to asymptomatic bacteriuria in pregnancy and further data in this hard-to-study population should be a primary concern for researchers. Incomplete voiding represents the primary risk factor for UTIs associated with conditions such as urinary incontinence and prolapse. Correcting the presence of residual urine remains the most effective prophylaxis in these populations. Bladder function alters throughout life; however, changes in function may be particularly profound in clinical populations at high risk of UTIs. Patients with neurogenic bladder will also likely have other evolving medical issues which increase the risk of UTIs, such as repeated catheterization and increasing residual urine volume. More aggressive antimicrobial prophylactic strategies may be appropriate in these patients. Again, the paucity of data on prophylaxis in these high-risk patients requires the attention of the research community.

Keywords: asymptomatic bacteriuria, catheterization, genital prolapse, incontinence, neurogenic bladder dysfunction, pregnancy, risk factors, urinary tract infections

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Introduction

The following narrative review is based on presentations from the 2^o Foro en Infecciones Urinarias Recurrentes (FIUR2) symposium, a Latin American forum to discuss current trends and challenges in treating recurrent urinary tract infections. The literature herein was compiled based on non-systematic review of the current literature and the expertise of the authors/presenters. Risk factors for urinary tract infections (UTIs) may be behavioral, anatomical, or genetic in nature, and will vary depending on both the population being considered and the

form of UTI. Transient conditions such as pregnancy may predispose to UTI or increase the risk of serious complications from infection. In permanent conditions such as neurogenic bladder dysfunction due to spinal cord injury, the evolving nature of the patient's needs and medical interventions mean that the risk of UTI changes over time. Improved practices (better hygiene or the avoidance of catheters, for example) can control for modifiable risk factors, while in the case of nonmodifiable risk factors the use of prophylactic therapies may be advisable.

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Risk factors for recurrent UTIs

A recurrent UTI refers to the occurrence of more than two symptomatic episodes within 6 months or more than three symptomatic episodes within 12 months.¹ Understanding the risk factors associated with recurrent UTI can help physicians tailor prophylactic strategies to effectively reduce the potential for recurrence. Risk factors form a key part of the classification system of UTIs.² Risk factors for recurrent uncomplicated UTI can be broadly split into those related to premenopausal women, and those related to postmenopausal women. The level of evidence for individual proposed risk factors in both groups varies, and myths about risk and erroneous risk-avoidance behaviors persist among both patients and physicians alike. Treatment of asymptomatic bacteriuria (ABU) in patients with recurrent UTIs has been shown to increase the risk of subsequent symptomatic UTI episodes and is therefore not recommended for this patient group.^{3,4}

Premenopause

Risk factors in premenopausal women include sexual intercourse, changes in bacterial flora, history of UTIs during childhood or family history of UTIs, and blood group. Specific risk factors related to sexual intercourse include frequency (four or more times per week), the use of spermicides that may alter vaginal pH and thus affect its flora (particularly the *Lactobacilli* component), and engagement with a new sexual partner within the last year.⁵ In a prospective study there was a high incidence of symptomatic UTIs among sexually active young women; this was strongly and independently associated with recent sexual intercourse and use of a diaphragm with spermicide, as well as with a history of recurrent UTIs. Lack of postcoital urination, vaginal douches, use of hot tubs, restrictive underwear, and the hygiene and circumcision status of male partners have been proposed as risk factors, but lack an evidence base.^{5,6}

A number of factors relate to family history and genetic predisposition. A greater predisposition for vaginal colonization by uropathogens appears to run in families, potentially due to the increased ability of bacteria to adhere to the epithelium due to an increased expression of *Escherichia coli* (*E. coli*) receptors on vaginal epithelial cells.⁷ An additional genetic factor which aids binding of uropathogens is related to a patient's blood group. Susceptibility appears to be related to secretor status. The vaginal epithelia of 'nonsecretor'

women express two extended-chain glycosphingolipids, which in turn bind to pathogens more avidly, increasing risk of infection. The effect on uropathogen binding is estrogen-dependent, hence the relationship with hormonal status.^{5,6,8,9} In addition, mouse and human data suggest that genetic polymorphisms which regulate the efficiency of the innate immune system are central to familial history of UTI.¹⁰

Postmenopause

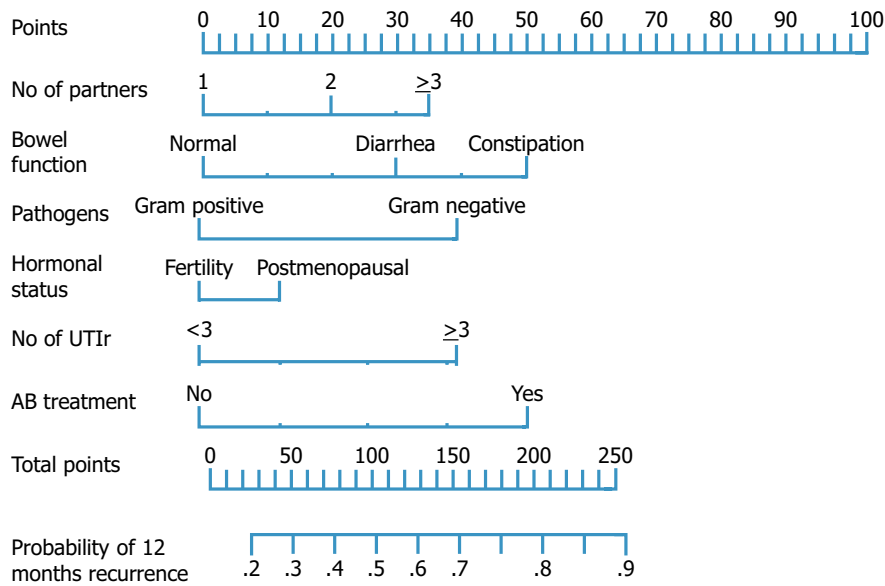
Postmenopausal patients share sexual intercourse and blood group as risk factors for recurrent UTIs with premenopausal patients.^{11,12} As would be expected, a history of UTIs during premenopause increases postmenopausal risk of recurrence. Vulvovaginal atrophy is also a risk factor in this group due to the relationship between estrogen, glycogen production, and colonization by *Lactobacilli*, all of which are reduced following the menopause. *Lactobacilli* colonization decreases pathogen colonization through the production of lactic acid *via* glucose metabolism, which decreases the vaginal pH.^{13,14} In addition, factors such as urinary incontinence, anterior vaginal wall prolapse, increased postvoid residual urine volume, and intermittent or permanent urinary catheterization predispose to complicated UTIs.

Nomogram for predicting recurrence risk

A recently published study modeled recurrence risk based on two Italian populations from different centers in Florence (2005–2009; $n = 768$) and Trento (2010–2012; $n = 373$). Using these data, a nomogram was produced to predict the likelihood of 12-month recurrence based on the most important risk factors identified: number of sexual partners, bowel function, pathogen type, hormonal status, UTI history, and history of previous antibiotic treatment (Figure 1).¹⁵

Asymptomatic bacteriuria in pregnant women

Diagnosis of ABU is based on the collection of two consecutive samples with the same bacterial strain with a quantitative count of $\geq 10^5$ colony-forming units/ml or a single catheterized urine sample with one bacterial species with a quantitative count of $\geq 10^2$ colony-forming units/ml.¹⁶ Bacteriuria primarily affects women (80% of cases) and is common in healthy individuals. In



To calculate the recurrence probability, identify patient values on each axis, then for each draw a vertical line upwards to the "points" axis. This determines how many points each variable generates. Add the points for all variables and locate this sum on the "total points" line. Then draw a vertical line downwards from this point and identify the recurrence risk probability at 12 months. No partners = number of partners in the last year; Bowel function = normal, chronic constipation, chronic diarrhea; Pathogens = type of pathogens isolated at the last UTI (Gram-positive or Gram-negative); Hormonal status = fertility status or postmenopausal status; No of UTI = number of UTI recurrences; AB treatment = previous treatment of asymptomatic bacteriuria. Figure from Cai *et al.* *Int J Urol.* 2014 Sep;21(9):929-34. © 2014 The Japanese Urological Association

Figure 1. Nomogram for the prediction of 12-month UTI recurrence risk.¹⁵ UTI, urinary tract infection.

young premenopausal nonpregnant women, the prevalence of ABU is between 1% and 5%. Prevalence increases with age: in elderly women aged 68–79 years, the prevalence is 13.6%, increasing to 22.4% in those aged 90 years and over.¹⁷ Treatment for ABU is not indicated for healthy premenopausal nonpregnant women, patients with pyuria, women with diabetes mellitus, the elderly, people with spinal cord injury, and patients with an *in situ* catheter.^{16,18} Neither is there any benefit to treatment in young patients, kidney transplantation, minor urologic procedures, nor prior to orthopedic surgery.^{3,16,18}

Several features of pregnancy act as predisposing factors for ABU, including: increased progesterone, slowed peristalsis, urinary stasis in ureters, uterine growth, bladder displacement, and increased volume of residual urine.¹⁹ During pregnancy, ABU can become symptomatic and harmful to the unborn child. UTIs are one of the most common types of infections during pregnancy (15% of infectious events), and ABU, cystitis, and pyelonephritis are commonly diagnosed in obstetric patients.²⁰ In a study which took samples at 12 and 32 weeks, 12.9% of pregnant women had ABU, and the proportion of patients with ABU increased to 16.8% in women with

diabetes mellitus or gestational diabetes mellitus.¹⁹ In the clinic, 25–40% of ABU cases during pregnancy evolve into symptomatic UTI, and the risk of pyelonephritis due to untreated ABU may be up to 40%.²¹ ABU infections are associated with low birth weight and premature birth, and are considered to be a potential marker for the intensity of prenatal care.^{22,23}

Screening

The range of ABU prevalence in pregnant women is wider than in nonpregnant, premenopausal women (1.9–9.5% *versus* 1.0–5.0%); however, the frequency of recurrence of ABU is comparable between these groups. Lack of diagnosis during pregnancy remains the major issue for ABU in this patient group.¹⁶ Screening for ABU by urine culture should be performed during the first prenatal visit and repeated in the third trimester, as status may change throughout pregnancy. Screening and treatment of ABU decreases the incidence of pyelonephritis by 75%.²⁴ Periodic screening for ABU should also be carried out after antibiotic treatment. Currently, there is no recommendation to rescreen women with negative cultures at the later stages of pregnancy.¹⁶

Antibiotic treatment for asymptomatic bacteriuria

A study conducted in pregnant women at a public healthcare (IMSS) clinic in Mexico found that the susceptibility of asymptomatic *E. coli* bacteriuria to common antibiotics was low (ampicillin 27%, trimethoprim/sulfamethoxazole 40%).²⁵ A meta-analysis including 14 studies from 1960 to 1980 and 2000 patients, showed that antibiotic treatment for ABU was beneficial, and reduced the risk of pyelonephritis, low birth weight, and preterm delivery.²³ However, these conclusions should be interpreted with care due to the low quality of the included studies. Recent data show no association between ABU in pregnancy and preterm birth or growth restriction and calls into question the need for routine midtrimester screening.²⁶ The paucity of recent high-quality studies underlines the need for further research on ABU in pregnancy. Regrettably, clinical studies in pregnant women remain challenging due to regulatory barriers and questions regarding legal liability, necessitating more clarity to facilitate research for these patients.²⁷

With the above in mind, treatment of ABU with antibiotics demands extreme caution. Overtreatment is a real concern because of possible risks for the fetus, and because of bacterial resistance, which is becoming increasingly widespread.^{18,28} Antibiotics may alter fetal flora and delay early gastrointestinal colonization, inhibit bone growth and cause fetal tooth discoloration (tetracyclines), and interfere with development of the baby's immune system; they may also cause cardiovascular defects and cleft-lip/cleft-palate (trimethoprim).^{29,30} In addition, two Danish studies have shown that systemic antibiotic use during pregnancy is associated with child obesity, asthma, allergy, and obsessive-compulsive disorder.^{31,32}

The Infectious Diseases Society of America (IDSA) guidelines recommend 3–7 days of antibiotic treatment for ABU in pregnant women. Recommended agents include nitrofurantoin (100 mg/6 h), amoxicillin/clavulanic acid (250 or 125 mg/12 h), and cephalexin (500 mg/6 h).¹⁶ It is generally accepted that the optimal treatment regimen is a 7-day course, with the best cure rates being achieved with 7 days treatment (when compared with shorter regimens).³³ Single-dose, 3-day, and 5-day treatments are being explored, but it is recommended to give standard treatment until validated studies with shorter regimens are available. Due to the low quality and conflicting results of published studies, the 2017 European

Association of Urology (EAU) Guidelines on Urological Infections recommend that national recommendations are consulted for treatment recommendations for ABU in pregnant women.⁴

Atypical UTIs and bacterial vaginosis in pregnancy

Atypical UTIs are commonly caused by *Chlamydia trachomatis* (*C. trachomatis*) and *Neisseria gonorrhoeae* (*N. gonorrhoeae*).³⁴ Although 70% of chlamydia infections are asymptomatic, some infections may lead to urethral syndrome and pelvic infection.³⁵ *N. gonorrhoeae* infection is asymptomatic in 50% of cases, and may increase the risk of premature birth four-fold.³⁶ Other complications include the risk of infection of sexual partners, pelvic inflammatory disease, infertility, arthritis, and spread *via* the bloodstream. *C. trachomatis* infections are well treated with macrolides, and *N. gonorrhoeae* can be treated with ceftriaxone. *N. gonorrhoeae* exists in a pan-resistant form with no available treatments.²⁵

Continued use of vaginal soaps and sanitary pads are associated with changes in the vaginal flora. Although no validated evidence exists, an increased risk of vaginal infections is observed in clinical practice in women who use these products. Bacterial vaginosis is caused by the proliferation of anaerobic bacteria, and complications are similar to those seen in symptomatic infections; 25% of patients with bacterial vaginosis during pregnancy present with a UTI (odds ratio 2.21–3.05).³⁷ Complications of bacterial vaginosis (such as chorioamnionitis and endometritis) may lead to premature delivery, and oral metronidazole is the recommended treatment option. Screening is recommended in the first trimester, and post-treatment screening is also necessary due to the high relapse rate.³⁴

Genital prolapse

Pelvic prolapse (or genital prolapse) is the descent of the pelvic organs due to weakness of one of the pelvic floor layers.^{38,39} Weakness of the anterior, apical, or posterior pelvic wall results in bulging of the vaginal walls due to pressure of the pelvic organs. Between 11% and 14% of women will require an intervention for prolapse during their lives. Approximately 40% of patients with prolapse have voiding issues, resulting in increased risk of UTI. Anterior prolapse (cystocele) is the form of prolapse most

significantly related to UTIs. However, posterior prolapse (rectocele) can cause significant pressure on the urethra, resulting in voiding problems and increased UTI risk. Knowledge of the affected pelvic wall is important to define an appropriate treatment plan. Pelvic Organ Prolapse Quantification (POP-Q), the most recent prolapse scoring system, defines four stages of prolapse (stages I, II, III, and IV with increasing severity). Surgical intervention is indicated for symptomatic prolapse causing dyspareunia or foreign body sensation and for bladder outlet obstruction which is frequently related to UTIs. However, when prolapse does not cause voiding issues, it does not increase the risk of UTIs. In a study from southeast Nigeria, 76% of women with pelvic prolapse presented with ABU.⁴⁰ Treatment for ABU in patients with pelvic prolapse is indicated only in case of pregnancy or urinary tract surgery.

Increased risk of UTIs is primarily caused by alterations in voiding either in the presence or absence of surgical intervention. A history of pre-surgical recurrent UTIs is the most important risk factor for developing a UTI after treatment.^{41,42} Treatment for UTIs in women with prolapse who have good voiding has no effect, and is not indicated.³⁹ After a surgical intervention readmission to hospital and the length of any hospital stay are significantly associated with UTIs.⁴¹ Studies have shown that the presence of residual urine reflects a high risk of UTIs in women with urinary incontinence.^{42–44} Interestingly, data indicate that residual urine volumes as low as 30 ml can increase the risk for UTIs.³⁹

Urological conditions predisposing to infection

Like any organ, the bladder has its peculiarities. A smooth muscle organ that, uniquely, is under complete voluntary control of the cerebral cortex, the bladder receives extensive somatic and autonomic innervation. The innervation of the bladder generates a feeling of fullness despite volume changes occurring without changes in intraluminal pressure. Voiding and voiding inhibition are voluntarily controlled, and a single contraction is initiated and maintained until full emptying (400–500 ml at capacity). Direct effects of aging on the bladder influence the risk of UTIs, and include decreased capacity, reduced contractility, increased hyperactivity, and increased residual urine.

Urinary incontinence

Urinary incontinence is defined as an involuntary loss of any amount of urine. It is primarily a storage disorder that on its own does not cause infections; however, a UTI may result from incomplete voiding due to surgical treatment.³⁸ Urinary incontinence is generally defined as stress, mixed, or urgency incontinence, but other specific causes must also be considered (postural, insensible, coital, multifactorial, etc.) The disorder is mainly rooted in the relaxation of the muscles or contractility of the bladder. Treatment for urinary incontinence is not always warranted and can sometimes induce the onset of recurrent UTIs (e.g. Burch colposuspension in patients with stress incontinence).

Neurogenic bladder dysfunction

Lesions to the nervous system commonly cause bladder dysfunction. The location of neurological lesions will affect the symptoms and urodynamics of neurogenic dysfunction.⁴⁵ Typical sources of lesions leading to neurogenic dysfunction include spina bifida, multiple sclerosis, Parkinson's disease, cauda equina syndrome, stroke, head trauma, spinal cord injury, diabetes mellitus, heavy metal poisoning, acute infections, tumors of the spinal cord, syphilis, and benign prostate hyperplasia.

Neurogenic dysfunction predisposes to infection in a number of ways. Direct effects include altered filling and voiding, as well as detrusor hyperactivity. The management of neurogenic dysfunction through urethral catheter, suprapubic catheter, or nephrostomy also increase the risk of colonization and UTIs. Neurogenic bladder also predisposes to morphologic causes of infection like kidney stones or foreign bodies. As mentioned previously, there is an increased likelihood of infection with organisms other than *E. coli* in complicated forms of UTI, such as that associated with neurogenic dysfunction. The increased risk in patients with neurogenic bladder has been described as exponential. Unsurprisingly, there is a significant increase in the complexity of the infection and its treatment. Emptying systems may be required *via* diversion of the urinary tract or catheter placement. Failure of host defense mechanisms, malnutrition, and the use of antibiotics for unrelated conditions, also often need to be considered as part of the risk profile.⁴⁶

Differential diagnosis should consider uncomplicated cystitis, urethritis, hyperactive psychosomatic

bladder, interstitial cystitis, cystocele, and bladder outflow obstruction. Patients are likely to present with altered urination frequency, nocturia, incontinence related to both urge and overflow, UTIs, and acute (and potentially chronic) urine retention. Catheterization is common, along with its short-term (e.g. trauma, wrong placement, hematuria, UTIs) and long-term (e.g. colonization, urethral secretion, malignancy, kidney stones, hematuria, obstruction, stricture) complications. The EAU guidelines for neurogenic dysfunction of the lower urinary tract make a series of recommendations, the most important of which is that in these patients, ABU should not be treated with antimicrobials.⁴⁷ Management of urinary tract dysfunction is the key strategy to prevent UTIs in patients with neurogenic bladder. Data are currently negative or inconclusive for prophylactics such as cranberry extracts and L-methionine in these patients. Long-term antimicrobial therapy may be considered, but with caution due to the risk of resistance. Current EAU guidelines state that vaccination therapy has yet to be tested in neurogenic patients.⁴⁸ However, in a single 6-month double-blind placebo-controlled crossover trial of OM-89 ($n = 70$) in neurogenic patients with chronic lower UTIs, immune-prophylaxis decreased the incidence of infectious episodes and the use of antimicrobials.⁴⁹

Alterations to the urothelium and UTIs

The urothelium is a thin transitional tissue, having a flat or layered structure depending on whether the bladder is distended or empty. Pathological changes related to neurogenic dysfunction, diabetes mellitus, and overactive bladder may result in trabeculated bladder, hyperemic bladder, or bladder diverticulum. Such changes can be identified *via* an abdominal ultrasound showing significant thickening of the bladder wall.

Multiple etiologies may lead to the thickening and loss of elasticity that defines bladder trabeculation. Obstruction of emptying is a typical cause. Hyperactive bladder is another cause of trabeculation in both sexes in the presence or absence of obstruction. A nonobstructed bladder with a hypoactive detrusor, or a neuropathic bladder, may also result in trabeculation. In children with enuresis related to morphologic changes in the detrusor muscle, early trabeculation may be observed. The most important morphologic change in bladder trabeculation is an increase in connective tissue, leading to muscle hypertrophy and full denervation of the urothelial and suburothelial neurons; this is due

to the inability of neurons to stretch sufficiently. The result is incomplete bladder emptying.⁵⁰

The electrical coupling to the detrusor muscle in the normal bladder allows voluntary control and inhibits unwanted micturition due to trivial electrical impulses. Increased coupling in an unstable bladder increases excitability, leading to uninhibited contraction in response to low intensity efferent stimuli.⁵⁰ In neurogenic bladder, disruption of the urothelium is accompanied by edema, cytokeratin production, and formation of collagen.^{51,52} In addition to these structural changes, repeated infection in these high-risk patient groups generally results in morphological changes to the urothelium. Rapid inflammation, edema, infiltration of cells by bacteria, bacterial accumulation, and bullous edema result in the production of bulli at the level of the mucosa. Chronic inflammation, urothelial cell apoptosis, and impaired barrier function are thought to be related to recurrent UTIs.^{53,54} The dynamic changes in bladder and overall function in this patient group require an equally dynamic management strategy. This must cover prophylaxis and treatment, and account for evolving levels of risk with different interventions over time.

Catheterization

Failure in infection prevention and control in patients with comorbid conditions often starts with indwelling urinary catheterization. Poor hand hygiene, poor aseptic technique, and poor catheter placement all predispose towards UTIs. Unnecessary or overlong catheterization is a further risk factor, with poor urethral orifice sepsis a predisposing factor. The formation of biofilms on catheters following catheterization is inevitable. Bacterial colonization is faster within the catheter lumen (48 h) than on the catheter's external wall (72–168 h).⁵⁵

The use of urinary catheters is the most common source of infections and Gram-negative bacteremia in the hospital setting. Incidence of bacteriuria and UTIs are a function of the duration of catheterization. After 3 days, 100% of patients with an open-drain system will have ABU, and 3–6% of patients will develop ABU per day of closed-drain catheterization. There is a 1–2% risk of infection with a single one-day catheter placement; the risk increases by approximately 10% with each additional day of catheter placement in women, and by approximately 3–4%

with each additional day of placement in men.⁵⁵ Long-term catheterization may lead to a failure of natural defense mechanisms and the creation of a reservoir of bacteria *via* biofilm formation. However, intermittent catheterization can reduce risk of symptomatic UTIs and lower the incidence of ABU. After a single intermittent catheterization, the rate of ABU is 3–5%, and symptomatic UTIs are rare. In intermittently catheterized patients with spinal injuries the prevalence of ABU is 50%, and the incidence of symptomatic UTIs is 0.41–1.86 episodes per 100 patient-days.⁵⁶ A short course of antibiotics may be necessary to control bacteriuria after catheter removal; however, guidelines recommend a urine culture before initiating treatment.⁴

Host characteristics which increase the risk of catheter-associated UTIs include urinary stasis, local trauma, anatomic or functional abnormalities of the urinary tract, diabetes mellitus, immunosuppression, weakness, poor hygiene, and advanced age. Some factors are sex-specific, including decreased estrogen production and the anatomical length of the urethra in women. In men, voiding dysfunction with increased bladder pressure and elevated residual urine increases the risk of infection. Specific guidelines are available aimed at the prevention and control of catheter-associated UTIs. The 2017 EAU guidelines detail catheter modification and prophylaxis strategies for infection control.⁴

Conclusion

Appropriate preventive measures are the best tactic to alleviate the burden of recurrent UTIs. Risk factors need to be assessed in the general population and applied when assessing individual patients with recurrent UTIs. Frequent intercourse, vulvovaginal atrophy, change of the local bacterial flora, history of UTIs during premenopause or in childhood, family history, and a non-secretor blood type are substantiated risk factors for recurrent UTIs.

ABU is a condition with a high prevalence which is benign in most cases. When assessing ABU in pregnancy, where the risk of adverse outcomes is higher, physicians need to consider differential diagnostics, particularly if patients do not respond to initial treatment. Inappropriate antibiotic treatment of ABU during pregnancy can potentially affect both the mother and child. The difficulty in obtaining ethics committee approval for trials in pregnant

women remains a stumbling block in improving therapy and prophylaxis in this patient group.

In cases of urinary incontinence and prolapse, voiding disturbances are the primary risk factor for recurrent UTIs, which may be related to the baseline condition or be caused by treatment modalities. Where present, obstruction must be corrected to prevent future infections.

Bladder function changes throughout life, altering treatment priorities and risks associated with interventions. Changes in function may be particularly profound in clinical populations at high risk of UTI, such as patients with neurogenic bladder or other groups that undergo repeated catheterization. In such high-risk patient groups, more aggressive prophylactic strategies may be appropriate. There is a paucity of clinical trials assessing prophylaxis which needs to be addressed.

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Conflict of interest statement

Dr García Mora is a speaker for Allergan, Lilly Icos, Novartis, Ferring, Aspen, Vifor Pharma Group and Asofarma and a proctor for Medtronic and Boston Scientific.

Dr Naber has acted as an investigator, consultant or speaker for Basilea, Bionorica, Daiichi Sankyo, Enteris Biopharma, Helperby Therapeutics, Hermes, Leo Pharma, MerLion, Vifor Pharma Group, Paratek, Pierre Fabre, Roche, Rosen Pharma, and Zambon.

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Dr Storme has acted as a speaker for Vifor Pharma Group.

Dr Dehesa-Dávila is consultant or speaker for Grunenthal, Pfizer, Vifor Pharma Group and Boehringer Ingelheim.


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