REVIEW ARTICLE

DRUG-RELATED URINARY TRACT INFECTIONS

Łukasz Dobrek
DEPARTMENT OF CLINICAL PHARMACOLOGY, WROCLAW MEDICAL UNIVERSITY, WROCLAW, POLAND

ABSTRACT
Bacterial urinary tract infection (UTI) is the most common infection, both in outpatient treatment and in hospital settings. Clinically, UTIs are classified into lower or upper urinary tract infections and can be either episodic or recurrent, and either uncomplicated or complicated. A severe UTI can lead to urosepsis and septic shock, while recurrent episodes of uncomplicated UTIs are considered to be an important etiological factor for the development of chronic kidney disease.

The aim of this paper was to briefly discuss the classification, symptomatology and pathophysiology of a UTI and describe the rationale for the development of some drug-related urinary tract infections. The pathophysiology of a UTI is associated with multiple, anatomical and physiological dysfunctions that predispose infection, but there are also some iatrogenic factors, including the use of certain medications, that contribute to UTI development. Among drugs associated with an increased risk of UTI development one should mention immunosuppressants, agents affecting normal voiding processes and increasing the intravesical volume of residual urine, drugs promoting lithogenesis in the urinary tract with the subsequent favouring of urinary stone formation or drugs that reduce glucose reabsorption in the kidneys, causing glycosuria ("gliflozins").

Conclusions: Therefore, a UTI may also be a specific manifestation of adverse drug reactions and it should be taken into account in the monitoring and diagnosing of drug-induced disorders.

KEY WORDS: urinary tract, infection, adverse drug reaction

INTRODUCTION

A urinary tract infection (UTI) is a common clinical entity in daily clinical practice, especially for primary care physicians, but it is also a significant health problem in hospital-based settings. The estimates indicate that UTIs account for about 10-20% of infections treated in primary care and they are the cause of 30-40% anti-infective treatment in hospital settings. The disease particularly affects women and in general, 40% of them develop at least one UTI episode in their life [1].

UTI is caused by an infectious etiological agent. However, in some cases, the occurrence of an infection is facilitated by the patient's pharmacotherapy. Thus, urinary tract infections may be a urological manifestation of adverse drug reactions.

THE AIM

The aim of this paper was to discuss the basic general pathophysiological premises of urinary tract infection and contend the most important issues of drug-related infections of the urinary tract.

MATERIALS AND METHODS

English-language papers were search in PubMed-NCBI and Google Scholar databases. The various applied search terms included: "urinary tract", "infection", "cystitis", "pyelonephritis", "drug", "adverse drug reaction", "drug-induced urinary tract infections". During the query, combinations of the above-mentioned search terms were used with the quantifier "AND". Published articles on or after 2000 were selected, along with one valuable review from 1998, which was also included in the analysis.

REVIEW AND DISCUSSION

CLINICAL CHARACTERISTICS OF UTI AND BASIC PRINCIPLES OF TREATMENT

A UTI is caused by various etiological factors (viruses, bacteria, fungi), but in common clinical practice, a bacterial UTI is the most commonly observed. The inflammatory process may affect either the lower (urethra and bladder) or upper (ureters, kidneys) urinary tract, or both of these. The diagnosis of a UTI requires the demonstration of clinical symptoms of an infection affecting the lower urinary tract, with laboratory evidence of bacteriuria/pyuria and the absence of non-infectious processes that might produce the revealed disturbances [2]. Clinically, UTIs are classified as uncomplicated or complicated. An uncomplicated UTI develops in individuals who are otherwise healthy and without pathological conditions that could aggravate the course of inflammation. Acute cystitis (UTI of the lower

urinary tract) and acute pyelonephritis (located in the upper urinary tract) are included in this entity. Cystitis presents with dysuria (pain during urination), frequent and urgent urination and possible suprapubic tenderness. The consequence of cystitis, which spreads in a retrograde direction, ascending to the kidneys and their collecting system, may develop into acute pyelonephritis, usually manifested by a triad of fever, nausea and flank pain, with or without accompanying symptoms of cystitis [2]. The acute pyelonephritis may also develop as a result of hematogenous spread from an inflammation located outside the kidneys, however, this scenario is much less common and is usually possible in immunocompromised and debilitated patients. Acute pyelonephritis is classified as an uncomplicated UTI form, but in some cases the disease can contribute to acute kidney injury, papillary necrosis, renal or perinephric abscess, or the development of emphysematous pyelonephritis [3].

The complicated UTI is recognized in patients with additional structural or functional risk factors, compromising the urinary tract or host defence, including urine obstruction or retention (due to incomplete bladder emptying or resulting from congenital or acquired anatomical abnormalities or neurological complication), systemic diseases (e.g., diabetes), immunosuppression, renal failure, kidney transplantation, pregnancy or the presence of foreign bodies in the urinary tract (calculi, indwelling catheters, drainage tubes). These conditions increase the risk of a serious outcome of the UTI episode, compared to individuals without the identified risk factors. Moreover, increasing age is itself a risk factor of a serious UTI episode due to the physiological premises (especially in older men with an enlarged prostate or postmenopausal women with vaginal atrophy), but also due to the need of the hospitalizations or long-term medical institutionalization (e.g., a stay in an extended care facility for elderly patients) with accompanying catheterization and because of the immune senescence [2].

The vast majority of uncomplicated UTIs are expected to resolve spontaneously or with the standard treatment, recommended for this disorder. UTIs episodes may be recurrent, that means that the next uncomplicated, symptomatic UTI episode follows the resolution of the previous incident, often after the implementation of the appropriate treatment. In terms of time criteria, a recurrent uncomplicated UTI is defined as three or more episodes during the last 12 months or at least two infections within 6 months. Moreover, a recurrent UTI is also defined to be a bacterial reinfection (a recurrence with a different organism, the same organism within more than 2 weeks) or bacterial persistence (an infection with the same bacteria not being eradicated in the urine 2 weeks after sensitivity-adjusted treatment). The frequent recurrence of lower urinary tract inflammation is mostly observed in children with vesicoureteric reflux or young, sexually active women, and in older patients with either anatomical or functional disturbances leading to obstruction or neurological defects of the lower urinary tract [4].

Most UTI cases are treated in outpatients settings, but patients who present severe symptoms of infections (e.g., high and persistent fever, the developing of systemic inflammatory response syndrome) or those who do not respond to the standard treatment should be hospitalized. The goal of the therapy is to quickly remove the etiological factor (see below) responsible for the development of inflammation in the urinary tract, which leads to the relief of symptoms. The first-line choice is to use an initial, empirical anti-infective agents, and in the case of their ineffectiveness, possibly switching to a targeted therapy after pathogen identification. Maintaining the adequate hydration of the patient, unless there are contraindications (e.g., urinary tract obstruction, the risk of fluid retention), is a non-specific, recommended procedure. Increasing the forced diuresis is aimed at accelerating the elimination of bacteria, although it is associated with the risk of reducing the concentration of anti-infective drugs in the urine [5].

With such treatment, a clinical response is expected within 24 hours for cystitis and within 48-72 hours for pyelonephritis. The lack of the expected response to the implemented empirical treatment is an indication for the introduction of targeted therapy. In the initial treatment, according to the available data on the susceptibility of microorganisms in Europe, fosfomycin trometamol, nitrofurantoin and pivmecillinam are considered to be first-line drugs. Alternative drugs are fluoroquinolones (e.g., levofloxacin, ofloxacin, ciprofloxacin) or cephalosporins (e.g., cephalexin, cefuroxime, cefadroxil). Aminopenicillins, along with beta-lactamase inhibitors (e.g., amoxicillin-clavulanate), are now also considered as alternative drugs. In areas of known low resistance (>20%), trimethoprim should also be considered together with sulfamethoxazole. The detailed characteristic of UTI treatment is out of the scope of this review and recommendations in this regard can be found in the relevant guidelines [6].

However, due to the fact, that UTIs are characterized by diverse etiologic agents, relatively high rates of recurrence and the growing multi-drug resistance to the current anti-infective treatment, they are becoming a serious challenge and concern for medical professionals. The leading causative factor of uncomplicated UTI still remains *Escherischia coli*, but the increase in resistance of the pathogen is a growing concern. The increase in multidrug-resistant *Klebsiella* sp. or *Proteus* sp. strains, responsible for complicated UTIs is also observed [1,2]. For a long time, bacterial strains with extended-spectrum beta lactamases remained a worrisome problem for physicians treating patients with UTI. Another problem was the emergence of strains showing plasmid-mediated fluoroquinolone resistance. Moreover, today the usefulness of even carbapenems, polimyxins or glycopeptides, due to the growing, acquired resistance to these antibiotics, is rapidly decreasing. The outbreaks of bacteria "extremely drug-resistant" or even "pan drug-resistant", resistant to all currently used chemotherapeutics, are beginning to be observed around the world. The problem also occurs among the uropathogens responsible for the development of UTIs [7]. Therefore, it must be highlighted that the "golden era"

of currently, routinely used antibiotics is waning and there is a need for both novel anti-infective chemotherapeutics discovery and for the introduction of alternative therapies[2]. Some hopes are also associated with phytotherapy, including traditional Chinese herbs and the use of nutraceuticals containing cranberry or D-mannose, but no single compound or mixture has been identified so far as the effective approach in patients with UTIs [8]. Similarly, a meta-analysis of nine randomized clinical trials did not show the efficacy of probiotics in UTI patients compared to a placebo, but the conclusion is not certain due to significant methodological differences and the design of individual clinical trials [9].

THE OUTLINE OF URINARY TRACT INFECTIONS PATHOPHYSIOLOGY

Normal urine is a solution with a pH ranging from 4.5-8.0 and containing no pathological microorganisms perceived as the etiological factors of a UTI. A UTI is diagnosed as the detection of the pathogen found in urine, in the presence of the clinical symptoms of developing inflammation, mentioned above. The pathogen is quantitatively and qualitatively detected and identified in a sample of midstream urine. According to a commonly accepted definition, in the case of a bacterial-related UTI, the minimum threshold level of bacteriuria confirming the presence of a UTI is 10^5 colony forming units (CFU)/mL urine. However, there are also suggestions that recommend the diagnosis of a UTI in the presence of particular types of bacteria already starting from a count of 10^3 CFU/mL [10]. Of note, an asymptomatic bacteriuria may also be found. The term describes the presence of bacteria in the normally sterile urine, but passing without any clinically detectable UTI symptoms and without the obvious renal damage [11]. In women, it is defined in the two consecutive voided urine specimens with isolation of the same bacteria at 10^5 CFU/mL or more; in men the recognition is based on the single, clean-catch voided urine sample [5]. The entity may be transient or persist for a prolonged time and it is recognized mostly in healthy women (with increasing frequency with age) and men after the age of 50. Thus, the laboratory diagnosis of both symptomatic UTI and asymptomatic bacteriuria based on the microbiological demonstration of the increased amount of bacteria in a correctly collected midstream, voided urine sample or in direct bladder urine sampling is a "gold standard" of UTI diagnosis [2, 5, 10]. In addition to microbiological diagnostics, the routine, laboratory diagnosis of UTIs in everyday clinical practice involves performing a clean-catch dipstick leukocyte esterase test that enables the detection of urinary white blood cells at more than $10/mm^3$ and the demonstration of the presence of nitrites in urinalysis (as a result of the action nitrate-reducing bacteria) [5].

On a margin, it should be emphasized that recent studies showed that urine collected from the middle stream, free from accidental microbial contamination, or even taken directly by bladder puncture, is not an absolutely sterile solution. The urinary tract is inhabited by various microbiota and bacteriuria demonstrated in the diagnostic procedure of a UTI is only a part of the microorganisms hosted by the urinary tract. Standard microbiological diagnosis of a UTI based on a culture in urine and pathogens' antibiotic susceptibility ignores the presence of many bacterial species and intracellular colonies that are considered to reside in the urinary tract. Nowadays, the urinary presence of stable bacterial communities is regarded to be beneficial and of symbiotic character [12]. The enhanced urine culture techniques enabling the detection of resident bacterial flora in the bladders of adults females revealed the presence of *Lactobacillus* (15%), followed by *Corynebacterium* (14%), *Streptococcus* (11.9%), *Actinomyces* (6.9%) and *Staphylococcus* (6.9%) genera. Within each genus, the most frequently isolated species were *Lactobacillus gasseri*, *Corynebacterium coyleae*, *Streptococcus anginosus*, *Actinomyces neuii* and *Staphylococcus epidermidis*. Other isolated genera included *Aerococcus*, *Gardnerella*, *Bifidobacterium* and *Actinobaculum* [13]. Some gender differences related to urinary residual flora were also detected. Another study demonstrated that the urine of healthy men contained no *Micrococcus* sp., *Streptococcus* sp., *Candida* sp., or *Bacillus* sp., but these genera were present in female urine. In female urine species *Lactobacillus* sp., *Peptococcus* sp., and *Propionibacterium* sp. were also found, and male urine species mostly contained *Eubacterium* sp. Moreover, the urine of healthy women contained no *Megasphaera*, *Mobilluncus* sp., or *Fusobacterium* sp., while the urine of healthy men contained no *Lactobacillus* sp., *Prevotella* sp., or *Actinomyces* sp. [14]. To sum up, the definition of a UTI is being changed and in the currently introduced paradigm of physiological urinary microbiota, a UTI is more likely to be understood as urinary tract dysbiosis [12]. The infringement of normal urinary microbiota, and the physiological microflora of the vagina or the digestive system occurs in patients treated with antibiotics exhibiting a broad-spectrum antibacterial activity, which further contributes to the development of multi-drug resistant microorganisms [2].

The main etiological factors of a UTI are both Gram-negative and Gram-positive bacteria; fungal (*Candida albicans*) or viral (adenoviruses) infections of the urinary tract are rare and generally occur in immunosuppressed patients. The most common reason of a UTI development is *Escherichia coli*, especially uropatogenic strains of *Escherichia coli* (UPEC), which is the causative factor of both uncomplicated and complicated UTI episodes. In complicated infections, the share of other Gram-negative microorganisms such as *Proteus mirabilis*, *Klebsiella pneumoniae* and *Pseudomonas aeruginosa* increases significantly. Of the gram-positive bacteria, UTIs are most often caused by *Staphylococcus saprophyticus*, *Enterococcus faecalis*, *Staphylococcus aureus* or *Streptococcus agalactiae*. The rarely identified bacterial etiological factors of a UTI are: *Corynobacterium uraelyticum*, *Aerococcus* spp., *Gardnerella vaginalis*, *Haemophilus influenzae* and some anaerobic bacteria, including *Bacteroides fragilis*, *Prevotella* spp., *Porphyromonas* spp., *Clostridium* spp. [2, 5, 6].

The most usual pathomechanism of a UTI can be described based on the scenario of the ascending infection starting from periurethral contamination of a pathogen, with subsequent colonization of the urethra and finally reaching the bladder. The complex phenomena, including the mechanisms of the pathogen itself and the patient, and the host-pathogen inflammatory interactions determine the further consequences and possible scenarios for the development of a UTI as an uncomplicated or complicated infection. The bacterial expression of pili, fimbriae and adhesins enables the adherence, tissue penetration and colonization of the bladder epithelium (urothelium), which is composed of "umbrella cells" (which form a layer of uroplakins on their apical membrane), and deeper lying intermediate and basal cells [2]. In some cases, when bacteria are insensitive to host defence mechanisms (e.g., neutrophil resistance), biofilm formation occurs. Biofilm is a special microenvironment for microorganisms, which effectively protects bacterial cells against opsonization and phagocytosis, as well as against the action of anti-infective chemotherapeutic agents, and creates optimal conditions for further pathogen differentiation and dispersion (detachment of biofilm fragments in order to colonize new life surfaces). Uropathogens disrupt the urothelium by releasing toxins and proteases to release nutrients from the bladder's cells and produce siderophores to obtain iron [2]. Finally, bladder epithelial damage develops as a result of persistent exposure to bacterial toxins. Ultimately, the presence of bacteria surviving in the lower urinary tract, with impaired patient defence mechanisms and maintaining of the essential mechanisms of uropathogens, enables the ascending colonization of the renal epithelium and its damage as a result of a release of tissue-damaging toxins. A detailed description of the pathogenesis of a UTI is out of the scope of this review and can be found in selected, synthetic and narrative reviews referring to that issue [15]. The most serious consequence of an ascending UTI, which is directly life-threatening, may be the development of bacteraemia – sepsis and, consequently, septic shock. It results from the fact that uropathogens may cross the tubular epithelial barrier, which is characterized by increased permeability in inflammatory conditions, and entering the blood stream. It triggers the complex inflammatory patient's response to infection – systemic inflammatory response syndrome (SIRS), leading to possible multiorgan dysfunction syndrome (MODS). Moreover, bacteria acting as pathogen-associated molecular patterns (PAMP) binding to pattern-recognition receptors (PRR) located on macrophages, neutrophils and endothelial cells, contribute to the release of pro-inflammatory mediators (NF-κB, Il-6, Il-12), initiating a "mediator storm", including potent vasodilatory TNF-α, with the subsequent production of later released chemokines, prostanoids or high-mobility group protein B1 (HMGB-1). The accumulation of vasoactive pro-inflammatory mediators may ultimately lead to hypotension and hypoperfusion and finally the development of septic shock [16].

URINARY TRACT INFECTIONS AS ADVERSE DRUG REACTIONS

Among the potential etiological factors of a UTI one should also mention the administration of certain drugs, since a UTI may also develop as an adverse drug reaction (ADR). According to the current Polish legislation (the Pharmaceutical Law Act of 6 September 2001; with subsequent amendments), an ADR is briefly defined as any unfavourable and unintended effect of a medicinal product (the key meaning for the diagnosis of ADR is the demonstration of a cause-and-effect relationship between the administered drug and the occurrence of the above-mentioned adverse consequence). Previously, an ADR was defined by the WHO as a response to a drug that is noxious and unintended, and which occurs at doses normally used in man for prophylaxis, diagnosis or the therapy of a disease, or for the modification of physiologic function [17]. Also, an acceptable definition of an ADR is the one given by Edwards and Aronson [18], according to which it is a harm directly caused by a drug at normal doses. The main mechanisms responsible for the development of ADRs are immune reactions (allergic reactions classified according to Gell-Coombs into 4 subtypes), reactions dependent on the dose and the pharmacological action of the drug, idiosyncratic and intolerant reactions, pseudoallergic reactions, and drug interactions [19]. Taking into account the fact that most drugs and their metabolites are excreted in the urine (renal clearance is the most important component of their total clearance), the kidney and urinary tract are especially predisposed to potential drug damage. With an efficiently functioning excretory system, drugs are quickly eliminated. However, the literature describes specific drug-induced urological and nephrological problems caused by selected drugs: renal calculi formation and crystalline nephropathy, erectile dysfunction, urinary retention or incontinence, interstitial nephritis, drug-induced glomerulonephritis, hemodynamic-induced kidney hypoperfusion or even acute kidney injury (e.g., contrast-induced acute renal failure) [20,21].

There are also drugs predisposed to the development of UTIs. The main mechanisms accounting for a drug-induced UTI include: immunodeficiency in the lower urinary tract (as a results of systemically acting immunosuppressive drugs), the impairing of micturition and bladder emptying (due to the cholinolytic activity or increasing of the bladder outlet resistance evoked by some drugs), urine stagnation and retention secondary to urinary stone formation in the urinary tract and intensification and promotion of bacterial colonization of urine, (as a result of drugs that intensify glycosuria). The examples the above-mentioned drugs are given in Table 1.

IMMUNOSUPPRESSANTS POSING A RISK OF INCREASED COLONIZATION OF THE URINARY TRACT BY PATHOGENS

Immunosuppressive drugs are a heterogenous group of agents that suppress the effector mechanisms of the immune system, including both cellular and humoral re-

Table 1. Drugs predisposing to the development of urinary tract infections (UTI).

Drug class	Drug subclass	Examples of the drugs	Rationale related to the increased risk of UTI development
Immunosuppressive agents		glucocorticoids cyclophosphamide azathioprine cyclosporin A sirolimus – rapamycin interferons mycophenolate mofetil	immunosuppression, impairment of host defense mechanisms
Anticholinergic drugs	Tricyclic antidepressants	amitryptyline imipramine clomipramine	disruption of the voiding process; impaired contractility of the detrusor muscle
	Phenothiazine antipsychotics	thioridazine chlorpromazine promazine	
	Antispasmodics	oxybutynin hyoscine (scopolamine)	
	Antiparkinsonian agents	benzatropine benzhexol orphenadrine procyclidine	
	Histamine H1 receptor antagonists	diphenhydramine chlorphenamine promethazine	
	Anticholinergics used in the treatment of chronic airway disease	ipratropium tiotropium	
	Anticholinergics used in the treatment of overactive bladder	tolterodine propiverine	
Antiarrhythmic drugs class I		disopyramide flecainide	
Benzodiazepines		diazepam clonazepam	disturbances of micturition probably caused by detrusor muscle relaxation
Opioids		morphine	disturbances of the voiding reflex, either on spinal and supraspinal level; bladder compliance impairment, the increase in the tone of the urethral sphincter
Non-steroidal anti-inflammatory drugs (NSAID)		mostly COX-2 inhibitors	impairment of the synthesis of micturition-stimulant prostaglandins which physiologically cause the release of tachykinins, which in turn stimulate the voiding reflex via neurokinin receptors located on afferent nerves and detrusor muscle
Calcium channels antagonists		flunarizine	decrease in smooth muscle contractility, including the detrusor, due to inhibition of calcium influx
Pseudoephedrine			elevation of tonus of the internal sphincter and proximal urethra, exacerbating voiding, due to the binding to alpha 1A/D adrenoreceptors

Drugs and their metabolites that may precipitate in the urinary tract	sulphonamides ciprofloxacin indinavir ampicillin antacids	crystallization of drugs and their metabolites in the urinary tract or inducement of the metabolic disturbances leading to the crystallization of endogenous lithogenic substances in the urinary tract, with subsequent disturbance of urine outflow due to the formation of urinary stones
Drugs that cause metabolic disturbances contributing to the precipitation of endogenous lithogenic substances in the urine	calcium vitamin D laxatives loop diuretics (furosemide) anhydrase inhibitors (acetazolamide) xanthine oxidase inhibitors (allopurinol) ascorbic acid	
Gliflozins – inhibitors of renal sodium-glucose transport proteins 2 (SGLT2)	canagliflozin dapagliflozin empagliflozin ipragliflozin luseogliflozin	increase of glycosuria, with subsequent bacterial colonization of urine

sponses. The immunosuppressants include glucocorticoids, cytostatic drugs (cyclophosphamide, azathioprine), drugs that act on immunophilins (cyclosporin A, sirolimus – rapamycin), antibodies or other agents (interferons, mycophenolate mofetil). These drugs are used in transplants (e.g., in renal transplant patients to prevent and treat rejection), oncology or in autoimmune disorders treatment. Their use is accompanied by undesirable effects, the most common of which is the increased risk of serious infections, including those caused by opportunistic microorganisms and possibly involving the urinary tract [22]. The incidence of a UTI varies among organ transplant recipients. In the Spanish Network for the Study of Infections in Transplantation clinical study the incidence (cases of infection per 100 recipients) of cystitis was estimated at 13.84 for kidney, 3.09 for liver, 2.41 for heart and 1.36 for lung transplant patients. Moreover, in the same study, the incidence of pyelonephritis was estimated at 3.66 for kidney, 0.8 for liver, 0.6 for lung and 0.3 for heart transplant recipients [23]. Thus, a UTI is considered to be the most common infection after kidney transplantation and its prevalence in kidney transplant recipients varies widely from 23% to even 75% [24]. In one retrospective study, the general incidence of a UTI in renal transplant recipients was estimated at 34.2%. Both *Escherichia coli* and *Klebsiella pneumoniae*, for both isolated and recurrent UTIs, were the most common infectious agents [25]. Moreover, the occurrence of a UTI in the early post-transplant period is associated with an increased risk for acute kidney rejection and impaired graft function [26]. In another, prospective study aimed at assessing bacterial and fungal infections in the early post-transplant period in 245 recipients during the first month after kidney transplantation, Gram-negative and Gram-positive bacteria were isolated in 56.4% and 35.7% of urinary specimens, respectively. Fungal strains were found in 7.9% of urinary specimens. The authors concluded that

urinary samples were predominantly microbiologically positive, compared to blood or respiratory specimens that were also collected from the study patients [27]. Therefore, it should be concluded that iatrogenic immunodeficiency resulting from the use of immunosuppressants is a significant risk factor for the development of a UTI. However, it is not the only factor in the development of a UTI in transplanted patients. Other pre-transplant factors (urine flow impairment, female gender, diabetes), as well as peri-transplant (bladder instrumentation, deceased donor grafts) and post-transplant (surgery-induced vesicoureteral reflux, reduced graft function) abnormalities also contribute to the development of a UTI in these patients [28].

DRUGS AFFECTING MICTURITION AND REDUCING BLADDER EMPTYING

Another group of drugs predisposed to the development of a UTI are drugs that impair the emptying of the bladder and contribute to postvoidal residual urine. UTI episodes may more easily develop under the resulting conditions of prolonged urinary stagnation. These drugs, listed in Table I, include compounds with cholinolytic (anticholinergic) activity, such as antimuscarinic bronchodilators, neurogenic antispasmodics, tricyclic antidepressants and antipsychotic drugs. These drugs may impair the complex parasympathetic control of the micturition and the contraction of the detrusor muscle, thus affecting the voiding phase. Also, some antiarrhythmics, antiparkinsonian agents, benzodiazepines, opioids, calcium channel blockers or pseudoephedrine affect urinary flow due to the bladder muscle relaxant effect and extending the storage phase [20,29]. Thus, all of the abovementioned agents may contribute to the acute, emergency urinary retention that requires immediate intervention (e.g., catheterisation, prostatectomy, treatment with cholinesterase

inhibitors). More insidious onset can lead to painless, chronic retention that eventually may account for renal failure due to the elevation of the upper urinary tract hydrostatic pressure [30]. Elderly patients are expected to exert a higher risk for drug-induced urinary retention since they often suffer from additional disorders (e.g., benign prostatic hyperplasia, urethral stricture, diabetes, bed-rest or surgery), which reinforce the voiding disturbances. It should be emphasized, however, that this premise remains purely theoretical and there are no detailed clinical data confirming or contradicting the actual increased risk of developing UTIs during the use of the abovementioned drugs. Some observational studies suggest that concomitant drugs may be a causative factor in up to 10% of urinary retention episodes [29].

DRUGS CONTRIBUTING TO URINARY STONE DEVELOPMENT AND URINARY RETENTION

Certain drugs also listed in Table 1 can cause urinary crystallization with the possible subsequent development of urolithiasis, which is associated with an increased risk of obstructed outflow and stagnation of urine. There are two main mechanisms accounting for drug-induced kidney stone development: (1) some drugs and their metabolites crystallize in the urinary tract or (2) some drugs cause metabolic disturbances contributing to the crystallization of endogenous lithogenic substances that are physiologically present in the urine. The detailed characteristics of the pathophysiology of urolithiasis and the drug-induced urinary stones can be found in one of the previously published review [31]. The obstructed outflow of urine favours increased bacterial colonization. According to the general concept of UTI pathophysiology, the free outflow of urine and "washing out" of bacteria colonizing the lower urinary tract is an important factor in reducing the development of infections. Thus, disruption of this mechanism promotes UTI development [15].

GLIFLOZINS − DRUGS INCREASING THE CONCENTRATION OF GLUCOSE IN THE URINE

One of the relatively new classes of antidiabetic drugs are inhibitors of renal sodium-glucose transporters 2 (SGLT2) also called gliflozins (from the main suffix repeated in the names of individual compounds), which are derived from its precursor found in the root bark of the apple tree – phlorizin. Canagliflozin, dapagliflozin, empagliflozin and ertugliflozin are approved by the Food and Drug Administration (FDA) in the USA and those drugs are also used in Europe, and ipragliflozin, luseogliflozin and tofogliflozin are registered in Japan [32]. Under physiological conditions, glucose is filtered in the kidneys and since it is a highly hydrophilic compound, it must be transported into the renal tubular cells using active sodium co-transport systems. There are 2 widely recognized conveyors for the urinary glucose, called SGLT1 and SGLT2. The SGLT2 one is a high capacity and low affinity system expressed

at a high level in the apical membranes of the convoluted portion of the kidney proximal tubules, responsible for almost 90% of the reabsorption of the filtered glucose (it transports one ion of sodium per molecule of glucose). SGLT1, which is characterized by a low capacity and high affinity (transports two ions of sodium per molecule of glucose), is located in the distal segment of the proximal tubules and mediates a near complete urinary reuptake of the remaining load of glucose that escapes reabsorption by SGLT2 [33]. Gliflozins inhibit the activity of SGLT2, thus these drugs decrease the reabsorption of excessively filtered glucose in the kidneys in hyperglycaemic, diabetic patients and cause iatrogenic glycosuria. Gliflozins exert some favourable effects in diabetic patients, with the most important improvement of glycemia, but also including other complex mechanisms of renoprotection: reduction of both pre- and afterload (due to diuretic and natriuretic effects, lowering of blood pressure and arterial stiffness), delay of micro- and macroalbuminuria, correction of abnormal tubuloglomerular feedback (that reduces hydrostatic intraglomerular pressure and delays pressure damage of the nephrons due to diabetic hyperfiltration) [32-34]. Despite the undeniable benefits of using gliflozins in diabetes, treatment with these drugs is also associated with some side effects, including an increased risk of developing genitourinary tract infections. The other important gliflozin-induced ADRs are: volume-dependent hypotension, the increased risk of amputation of the toes of lower limb (most likely due to the volume depletion, haemoconcentration and possibly peripheral ischemia) , bone fractures (conditioned by increased tubular reabsorption of phosphates that finally triggers parathormone release and subsequent pathological bone remodelling), ketoacidosis development (since the increased glucose loss may diminish insulin secretion) [33-35]. The potential risk of a UTI occurrence was demonstrated for all gliflozins, which supports the need of the education of patients treated with these drugs to maintain appropriate hygiene and daily water intake to prevent a UTI. However, on the other hand, despite the strong pathophysiological rationale, the data referring to the incidence of UTIs obtained from clinical trials, provided conflicting results. Some meta-analyses of large clinical studies showed a significant increase in the higher risk of a UTI in patients treated with SGLT2 inhibitors [36,37], while other meta-analysis failed to demonstrate any relevant difference in UTIs between gliflozins and placebo [38,39]. Thus, the issue of real exposure to a UTI development during gliflozin therapy still requires further research. However, there is agreement on the observations showing a significantly increased risk of developing genital infection in patients receiving gliflozins since glucosuria also increases the glucose amount on genital skin. The female gender and the previous episodes of UTIs are the main predictors of the chance for an infection to occur. Genito-urinary tract infections are usually mild and do not require discontinuation of treatment with SGLT2 inhibitors [40]. The exception is a rare, but possible life-threatening complication, known as Fournier gangrene, character-

ized by a necrotizing infection of the external genitalia, perineum and perianal region (necrotizing fasciitis of the perineum) [35].

CONCLUSIONS

The etiological factors of a UTI also include the use of certain drugs that are predisposed to the development of urinary tract infections by disturbing the normal outflow of urine (drugs that interfere with the voiding process or those that contribute to the development of urinary stones), inducing immunosuppression or increasing the bacterial colonization of urine resulting from enriching the medium with glucose. Therefore, a UTI may be considered as one of the specific, adverse drug reactions affecting the kidney and urinary tract and it must be taken into account during pharmacovigilance studies and analysis. It must be emphasized that during pharmacotherapy with the use of many commonly drugs mentioned in the review, physicians should be vigilant for the possibility of a UTI development, and patients should be educated and monitored for symptoms suggesting a urinary tract infection for an early and proper diagnosis and treatment of the clinical entity.

REFERENCES

1. Stefaniuk E, Suchocka U, Bosacka K, et al. Etiology and antibiotic susceptibility of bacterial pathogens responsible for community-acquired urinary tract infections in Poland. Eur J Clin Microbiol Infect Dis. 2016;35:1363-1369.

2. Flores-Mireles AL, Walker JN, Caparon M, et al. Urinary tract infections: epidemiology, mechanisms of infection and treatment options. Nat Rev Microbiol. 2015;13:1-13.

3. Hudson C, Mortimore G. The diagnosis and management of a patient with acute pyelonephritis. Br J Nurs. 2020;29:144-150.

4. Al-Badr A, Al-Shaikh G. Recurrent urinary tract infections management in women: a review. Sultan Qaboos Univ Med J. 2013;13:359-367.

5. Lee HS, Le J. Urinary tract infections. PSAP 2018 BOOK 1: Infectious Diseases; p. 7-28 (online) 2018 [download: 05.11.2020]. https://www.accp.com/docs/bookstore/psap/p2018b1_sample.pdf

6. Pujades-Rodriguez M, West RM, Wilcox MH, et al. Lower urinary tract infections: management, outcomes and risk factors for antibiotic re-prescription in primary care. EClinicalMedicine 2019;14:23-31.

7. Perletti G, Magri V, Cai T, et al. Resistance of uropathogens to antibacterial agents: emerging threats, trends and treatments. Arch Ital Urol Androl. 2018;90(2):85-93.

8. Cai T, Tamanini I, Kulchavenya E, et al. The role of nutraceuticals and phytotherapy in the management of urinary tract infections: what we need to know? Arch Ital Urol Androl. 2017;89(1):1-6.

9. Rondanelli M, Faliva MA, Perna S, et al. Using probiotics in clinical practice: where are we now? A review of existing meta-analyses. Gut Microbes 2017;8(6):521-543.

10. Schmiemann G, Kniehl E, Gebhardt K, et al. The diagnosis of urinary tract infection: a systematic review. Dtsch Arztebl Int. 2010;107(21):361-367.

11. Nicolle LE. Asymptomatic bacteriuria and bacterial interference. Microbiol Spectr. 2015. doi:10.1128/microbiolspec.UTI-0001-2012.

12. Lee SJ. Recent advances in managing lower urinary tract infections [version 1; referees: 2 approved]. F1000Research 2018;7(F1000 Faculty Rev):1964.

13. Hilt EE, McKinley K, Pearce MM, et al. Urine is not sterile: use of enhanced urine culture techniques to detect resident bacterial flora in the adult female bladder. J Clin Microbiol. 2014;52(3):871-876.

14. Kogan MI, Naboka YL, Ibishev KS, et al. Human urine is not sterile – shift of paradigm. Urol Int. 2015;94(4):445-452.

15. McLellan LK, Hunstad DA. Urinary tract infection: pathogenesis and outlook. Trends Mol Med. 2016;22(11):946-957.

16. Dreger NM, Degener S, Ahmad-Nejad P, et al. Urosepsis – etiology, diagnosis and treatment. Dtsch Arztebl Int. 2015;112:837-848.

17. Schatz SN, Weber RJ. Adverse drug reactions. PSAP CNS/Pharmacy Practice 2015;5-21.

18. Edwards IR, Aronson JK. Adverse drug reactions: definitions, diagnosis and management. Lancet 2000;356:1255-1259.

19. Smith W. Adverse drug reactions. Aust Fam Physician 2013;42:12-16.

20. Badyal K, Anton C, Ferner R. Adverse drug reactions and urological disease. Trends Urol Men's Health 2017;8(3):21-25.

21. Bartoli E. Adverse effects of drugs on the kidney. Eur J Int Med. 2016;28:1-8.

22. Crane A, Eltemamy M, Shoskes D. Transplant immunosuppressive drugs in urology. Transl Androl Urol. 2019;8(2):109-117.

23. Lopez-Medrano F, Aguado JM. Urinary tract infections in transplant recipients. Antimicrobe Infectious Disease and Antimicrobial Agents (online). [download: 05.11.2020]. http://www.antimicrobe.org/new/t32_dw.html

24. Parasuraman R, Julian K, and the AST Infectious Diseases Community of Practice. Urinary tract infections in solid organ transplantation. Am J Transplant. 2013;13:327-336.

25. Camargo LF, Esteves AB, Ulisses LR, et al. Urinary tract infection in renal transplant recipients: incidence, risk factors, and impact on graft function. Transplant Proc. 2014;46(6):1757-1759.

26. Fiorentino M, Pesce F, Schena A. Updates on urinary tract infections in kidney transplantation. J Nephrol. 2019;32:751-761.

27. Kawecki D, Wszola M, Kwiatkowski A, et al. Bacterial and fungal infections in the early post-transplant period after kidney transplantation: etiological agents and their susceptibility. Transplant Proc. 2014;46:2733-2737.

28. Gołębiewska J, Dębska-Ślizień A. Urinary tract infections in renal transplant recipients. In: Jarzembowski T, Daca A, Dębska-Ślizień MA, eds. Urinary tract infection – the result of the strength of the pathogen, or the weakness of the host (online). IntechOpen; 2018 p. 33-45. [download: 05.11.2020]. https://www.intechopen.com/books/urinary-tract-infection-the-result-of-the-strength-of-the-pathogen-or-the-weakness-of-the-host/urinary-tract-infections-in-renal-transplant-recipients.

29. Verhamme KMC, Sturkenboom MCJM, Stricker BHCh, et al. Drug-induced urinary retention. Drug Saf 2008;31(5):373-388.

30. Drake MJ, Nixon PM, Crew JP. Drug-induced bladder and urinary disorders. Drug Saf. 1998;19(1):45-55.

31. Dobrek Ł. Kidney stone disease with special regard to drug-induced kidney stones – a contemporary synopsis. Wiad Lek. 2020;73(9 p. 2):2031-2039.

32. Ansary TM, Nakano D, Nishiyama A. Diuretic effects of sodium glucose cotransporter 2 inhibitors and their influence on the renin-angiotensin system. Int J Mol Sci. 2019;20:629. doi:10.3390/ijms20030629.

33. Beitelshees AL, Leslie BR, Taylor SI. Sodium-glucose cotransporter 2 inhibitors: a case study in translational research. Diabetes 2019;68:1109-1120.

34. Gonzales DE, Foresto RD, Ribeiro AB. SGLT-2 inhibitors in diabetes: a focus on renoprotection. Rev Assoc Med Bras. 2020;66:17-24.

35. Garofalo C, Borrelli S, Liberti ME, et al. SGLT2 inhibitors: nephroprotective efficacy and side effects. Medicina 2019;55:268. doi:10.3390/medicina55060268.

36. Liu J, Li L, Li S, et al. Effects of SGLT2 inhibitors on UTIs and genital infections in type 2 diabetes mellitus: A systematic review and meta-analysis. Sci Rep. 2017;7:2824. doi:10.1038/s41598-017-02733-w.

37. Puckrin R, Saltiel MP, Reynier P, et al. SGLT-2 inhibitors and the risk of infections: A systematic review and meta-analysis of randomized controlled trials. Acta Diabetol. 2018;55:503-514.

38. Neal B, Perkovic V, Mahaffey KW, et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. N Engl J Med. 2017;377:644-557.

39. Wiviott SD, Raz I, Bonaca MP, et al. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. N Engl J Med. 2019;380:347-357.

40. Arakaki RF. Sodium-glucose cotransporter-2 inhibitors and genital and urinary tract infections in type 2 diabetes. Postgrad Med. 2016;128:409-417.

ORCID and contributionship:

Łukasz Dobrek – 0000-0001-5049-0026 [A,B,D-F]

Conflict of interest:

The Author declare no conflict of interest.

CORRESPONDING AUTHOR
Łukasz Dobrek
Department of Clinical Pharmacology,
Wroclaw Medical University,
Borowska 211A, 50-556, Wroclaw, Poland
e-mail: xlukaszx@onet.eu

A – Work concept and design, **B** – Data collection and analysis, **C** – Responsibility for statistical analysis,
D – Writing the article, **E** – Critical review, **F** – Final approval of the article