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UNIVERSITY OF SPLIT
SCHOOL OF MEDICINE

Selma Kastrat

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Diploma thesis

Academic year:
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Assoc. Prof. Ivo Ivić, MD, PhD

Split, July 2018

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1. INTRODUCTION

1.1 Urinary tract anatomy

The human urinary tract is a contiguous hollow-organ system and its primary function is to collect, transport, store, and export urine periodically and in a highly controlled manner. This way, the urinary tract ensures the removal of metabolic products and toxic wastes that collect in the kidneys. The constant urine flow in the upper urinary tract and the intermittent excretion from the lower urinary tract also plays an important part in cleansing the urinary tract, from microbes that might have already entered. Anatomically consisting of, from proximal to distal, of renal papillae, renal pelvis, ureters, bladder, and urethra, each component of the urinary tract has specific anatomic characteristics and performs critical functions (1) (Figure 1).

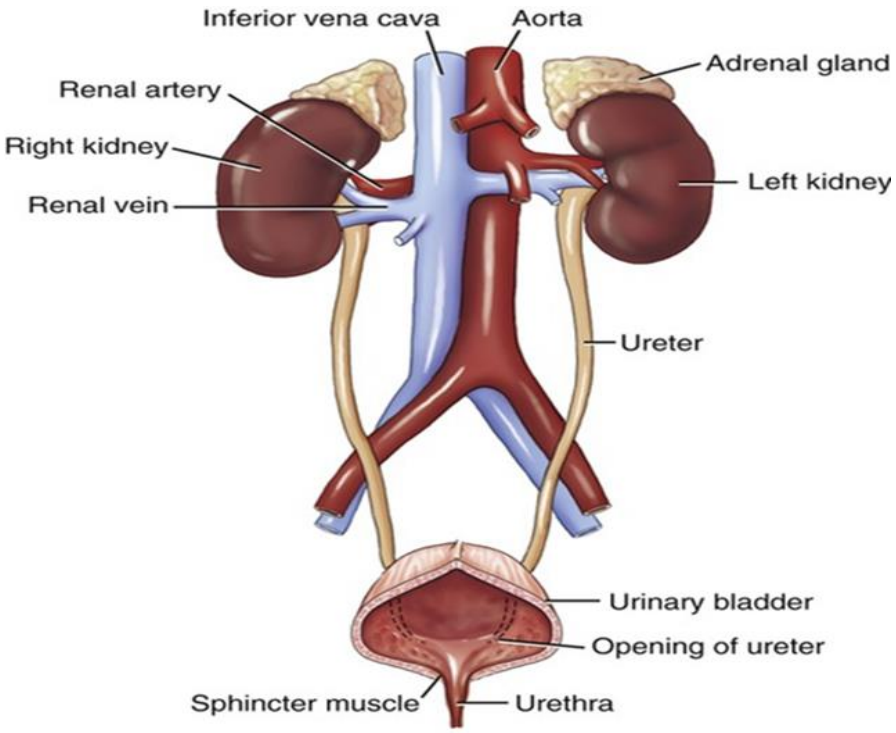

Figure 1. Anatomy of the urinary tract
Source from http://www.pharmatips.in/Articles/Human-Anatomy/Introduction-To-Anatomy-Of-Urinary-System.aspx

The upper urinary collecting system consists of renal papilla, into which each renal tubule-rich pyramid drains, and is considered as the first large structure of the upper collecting system. Renal papillae are individually curved by a minor calyx, and this in turn narrows into an infundibulum. Infundibuli vary in number, length, and diameter but connect to form either 2 or 3 major calyces. These connections are termed upper, middle, and lower-pole calyces

depending on which pole of the kidney they channel into. The renal pelvis represents the connection of these major calyceal branches and it can vary greatly in size and location (1).

The ureters are bilateral fibromuscular tubes that drain urine from the renal pelvis to the bladder. They mostly averge 22–30 cm in length and pass through the retroperitoneum. They arise behind the renal artery and vein at the ureteropelvic junction (UPJ), then they continue inferiorly along the anterior part of the psoas muscle. When the ureters enter the pelvic cavity they pass medially and cross in front of the common iliac artery. The ureters pierce the bladder wall obliquely at the ureterovesical junction or UVJ and travel in this direction for 1.5 to 2.0 cm within the bladder wall to cease in the bladder lumen as ureteral orifices. Along the ureter there are three segments that are physiologically smaller in diameter: the ureteropelvic junction, the ureterovesical junction, and where the ureters cross the common iliac artery. These three areas are clinically important as they represent the most common sites where ureteral calculi become fastened, causing obstruction (1,2).

The bladder is a hollow, distensible muscular organ that is tetrahedral when empty and ovoid when filled. It predominantly consists of smooth muscle and collagen and, to a much lesser degree, elastin (2,3). Its superior portion is marked by the urachus, which attaches the bladder apex to the anterior abdominal wall. In males the bladder lies between the rectum and pubic symphysis and in females, between the rectum and uterus/vagina. Another difference is that in males, the base of the bladder rests on the endopelvic fascia and the pelvic floor musculature, and the bladder neck is 3 to 4 cm behind the symphysis pubis where it is fastened by the endopelvic fasciae and the prostate. In this section, there is a layer of smooth muscle that surrounds the bladder neck and forms the involuntary internal-urethral sphincter. In females on the other hand the base of the bladder and urethra rest on the anterior wall of the vagina (Figure 2).

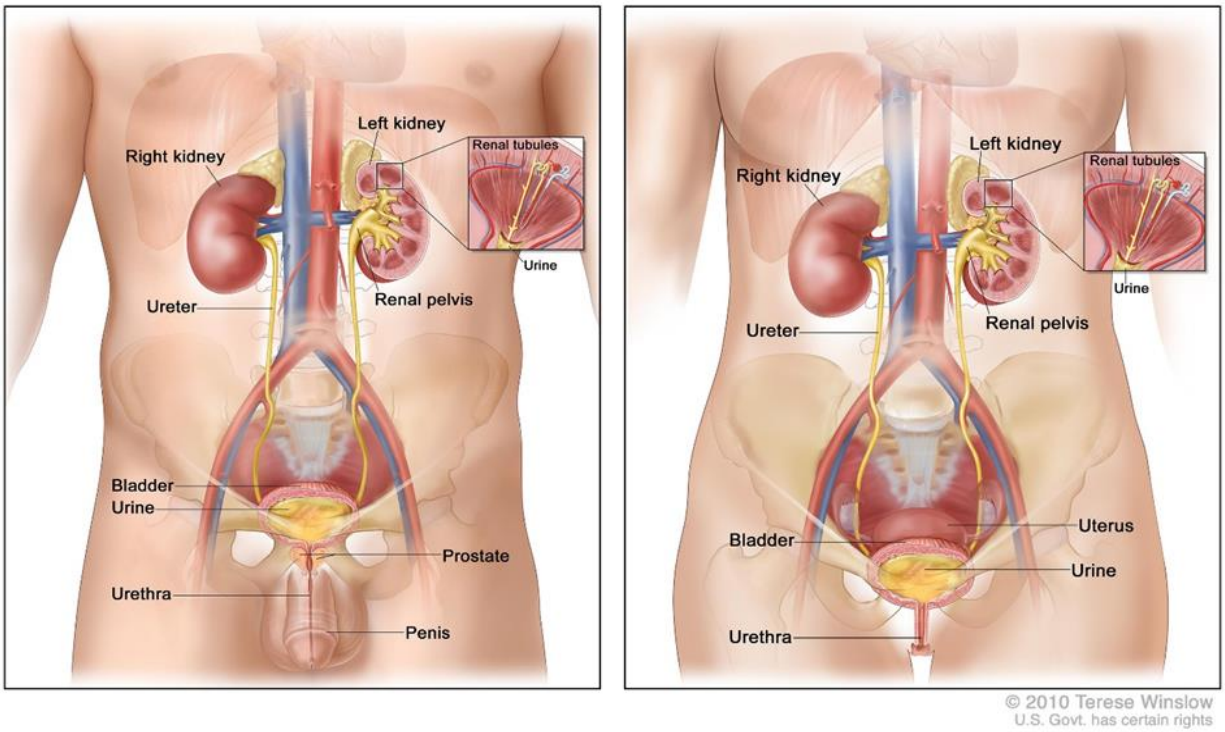

Figure 2. Anatomy of the male and female urinary system from left to right
Soure from http://anatomymedicalook.com/anatomy-of-a-womens-urinay-system/anatomy-of-a-womens-urinay-system-anatomy-of-a-womens-urinay-system-kidney-location-in-women/

The internal-urethral sphincter is not as well developed in females (4).The urethra begins at the distal end of the internal-urethral sphincter and is in continuation with the bladder. In males the urethra is mostly between 13 and 20 cm in length and is divided into prostatic, membranous, and penile portions. The prostatic urethra is 3–4 cm in length and runs through the length of the prostate. The membranous urethra spans 2 to 2.5 cm and this portion of the urethra is entirely surrounded by striated muscle known as the external-urethral sphincter. The penile portion of the urethra is contained within the corpus spongiosum and extends on an average of 15-cm, it dilates slightly in the glans penis (fossa navicularis) and ends at the external-urethral meatus. The female urethra is 3.8 to 5.1 cm long and is remarkably shorter than the male one, and passes obliquely from the bladder neck to external-urethral meatus along the anterior vaginal wall. The distal two-thirds of the female urethra are surrounded by a slow-twitch striated muscle termed the external-urethral sphincter (1,5) (Figure 3).

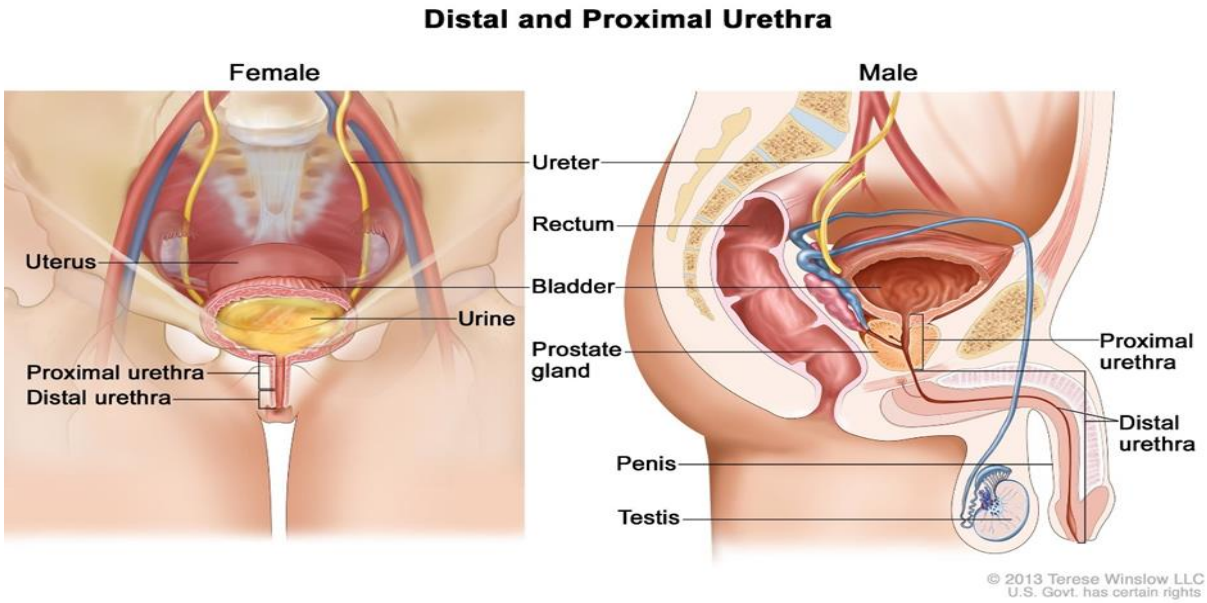

Figure 3. Anatomy of the female and male urinary tract with focus on urethra
Source from http://anatomymedicalook.com/anatomy-of-a-womens-urinay-system/anatomy-of-a-womens-urinay-system-female-urinary-tract-diagram-female-reproductive-and-urinary/

Although it is not a part of the urinary tract, the vagina plays an important role in the UTI pathogenesis. It is a fibromuscular organ lined by epithelial cells that extends from the opening of the labia minora (vestibule) to the uterus. The anterior wall is approximately 7.5 cm long and its posterior wall approximately 9 cm long. The anterior wall is in proximity to the bladder base superiorly and urethra inferiorly. Posteriorly, the vaginal wall is separated from the rectum by the recto-uterine pouch superiorly and by the Denonvillier's fascia and the perineal body inferiorly. The inner parts of the vagina are covered by a non-keratinized, stratified, squamous epithelium. At the onset of puberty the vaginal epithelium thickens and accumulates glycogen. The muscular layers consist of smooth muscle found that exists in both a longitudinal and circular orientation (1,6). In a reproductive women the normal vagina is colonized by the lactobacilli which produce lactic acid, producing a low pH condition which is unfavorable for the growth and colonization by uropathogenic microbes. This establishes one of the major host defenses, as alterations in these defenses are considered a key factor to UTIs (7).

1.2 Urinary tract infection

Urinary tract infections can be defined as a condition in which bacteria are colonizing and multiplying within the urinary tract. Urinary tract infections (UTIs) occur as a result of the

interaction of bacterial virulence and host biologic and behavioral factors, as opposed to highly efficient host defense mechanisms. There are three possible routes whereby bacteria can invade and spread within the urinary tract, the ascending, hematogenous, and lymphatic pathways. Diagnosis requires demonstration of bacteriuria defined as the presence of $\geq 10^5$ or more colony forming units (CFU) per ml of urine with symptoms. Exceptions to this include patients with pyogenic abscess of kidney or perinephric tissue, obstructed pyelonephrosis or bacterial prostatitis in whom the urine may be sterile (6,8).

Bacteriuria is a term that is used quite often and means, occurrence of bacteria in urine, while significant bacteriuria relates to the numbers of bacteria in voided urine that usually exceed the numbers caused by contamination from the anterior urethra, $\geq 10^5$/ml of urine (8,9).

Urinary tract infections can be anatomically distinguished into upper (kidney) and lower infection (bladder, prostate and urethra). This distinction can be useful as infections in the lower division of the tract commonly cause dysuria, frequency and urgency. While pyelonephritis (inflammation of the renal parenchyma) gives a clinical picture of chill and fever, flank pain and constituent symptoms due to bacterial invasion of the kidney. It is however important to remember that localizing the site of infection based on symptoms and signs can be inaccurate. With the help of urethral catheterization it has been detected that approximately 50% of women with asymptomatic bacteriuria had infection in their upper tracts, which confirms the inaccuracy of using symptoms for localization of infection (8,9).

Another distinction that is important and generally used for the best management of patients with urinary tract infections, is the one between uncomplicated infections and complicated. Uncomplicated urinary tract infections refer to episodes of cysto-urethritis, following bacterial colonization of the ureteral and bladder mucosae to infection, in a structurally and neurologically normal urinary tract. In general, the following definitions are used: an uncomplicated UTI is an episode of cystitis in a woman who is not pregnant, is not immunocompromised, has no anatomical and functional abnormalities of the urogenital tract, and does not exhibit signs of tissue invasion and systemic infection. Those infections that are accounted for as complicated are defined as ones that have an increased risk for complications. These include those involving the parenchyma (pyelonephritis or prostatitis) and frequently evolve in the setting of obstructive uropathy or after catheterization. The presence of

obstruction, stones or high-pressure vesico-ureteric reflux, perinephric abscess, life-threatening septicemia or a combination of these predispose to kidney damage. Infective episodes may also be refractory to therapy. Refractions often result in relapses and occasionally leads to significant complications such as sepsis, metastatic abscess and rarely acute renal failure (8,9) (Figure 4).

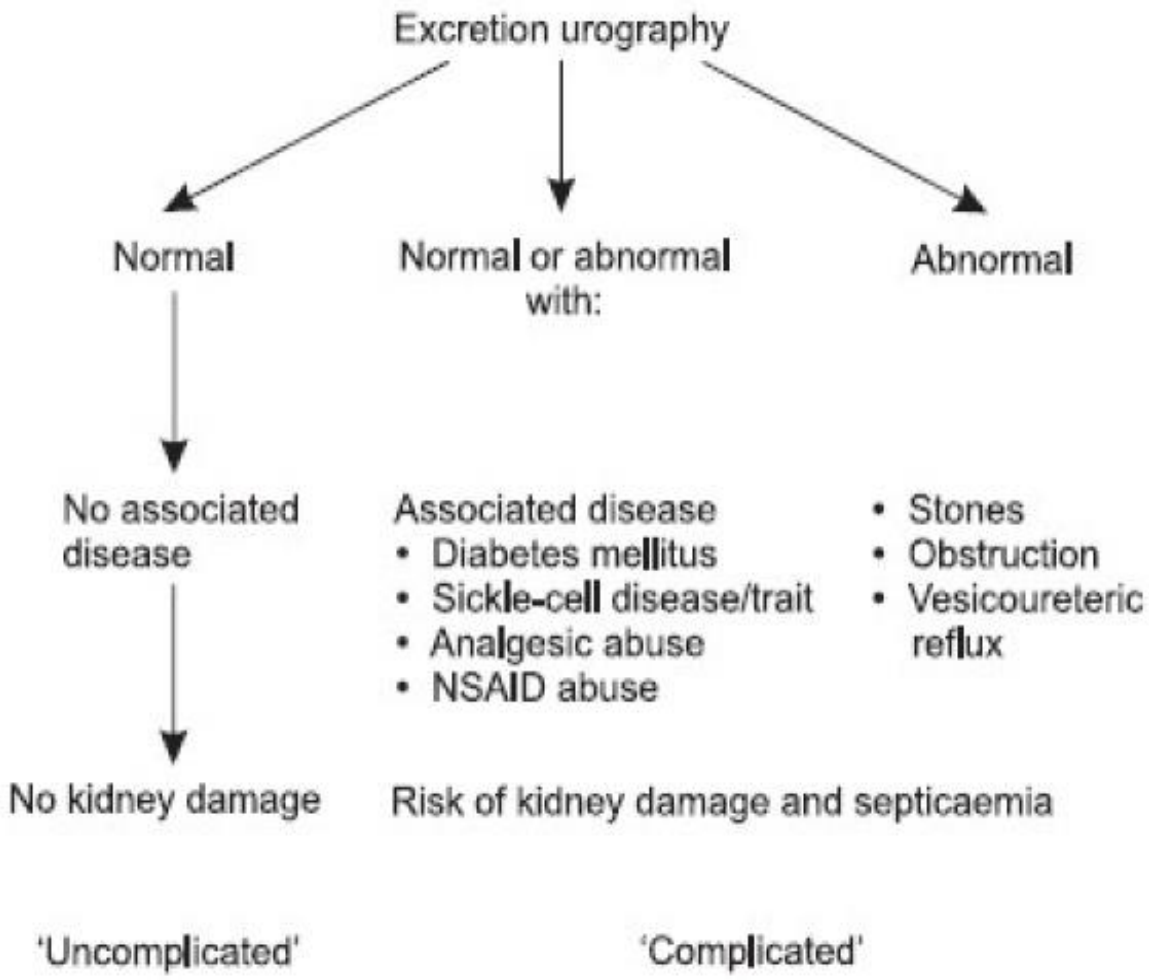

Figure 4. Classification of complicated and uncomplicated urinary tract infection

Source from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2875701/#CIT6

1.3 Pathophysiology of urinary tract infections

Bacteria are the most common cause of urinary tract infections. As previously mentioned, there are three possible routes whereby bacteria can invade and spread within the urinary tract, the ascending, hematogenous, and lymphatic pathways In healthy patients the route of infection is most often caused by uropathogens originating from rectal flora that are entering the urinary tract via the urethra into the bladder. This route is called ascending and

uropathogens attach to and colonize urothelium of the distal urethra. This particular route is at additional risk in patients with soiling around the perineum, in patients with urinary catheters and in females that use spermicidal agents. The fact that urinary tract infections are much more common in sexually active women than in men gives support to the importance of the ascending route of infection. The female urethra is short and is in proximity to the vulvar and perianal areas making contamination likely. It has been shown that the organisms that cause UTI in women colonize the vaginal introitus and the periurethral area before urinary infection occurs. Once within the bladder, bacteria may multiply and then pass up the ureters, especially if vesicoureteral reflux is present, to the renal pelvis and parenchyma (8–10).

Other differences in UTI prevalence between men and women result from a set of other factors, including the larger distance between the anus (the usual source of uropathogens) and the urethra in men, the dry environment around the male urethra and the antibacterial activity of prostatic fluid. Risk factors associated with UTI in healthy men include intercourse with an infected female partner, homosexuality and lack of circumcision but very often none of these factors is present in men with UTI (9,11).

In individuals with an intact health an infection of the kidney through the haematogenous route is uncommon. It does occasionally happen that the renal parenchyma may be breeched in patients with *Staphylococcus aureus* bacteremia or *Candida* fungemia that originate from oral sources in immunosuppressed patients. On other rare occasions bacteria from nearby organs may penetrate the urinary tract via the lymphatics. Conditions that spread via the lymphatic route are retroperitoneal abscesses and severe bowel infections (8,9).

1.4 epidemiology and etiology

Urinary tract infections (UTIs) are among the most commonly experienced infections by humans after respiratory and gastro-intestinal infections. In actuality, bacterial infections of the urinary tract are the most common cause of both community acquired and nosocomial infections for patients admitted to hospitals. It is a distressing infection and can at rare occasions even be life threatening (5).

The microbial etiology of urinary tract infections has for several decades been regarded as reasonably consistent. The predominant uropathogen that continues to be isolated in patients with acute uncomplicated cystitis and acute uncomplicated pyelonephritis is *E.coli* (10).

Although there is a great difference between the bacterial flora of the urine in patients with an initial episode of UTI compared with the flora from frequent recurrences of infection, *E.coli* is the most frequent pathogen in acute infection. In recurrent UTIs, especially in the presence of structural abnormalities in the urinary tract (e.g., obstructive uropathy, congenital anomalies, neurogenic bladder, and fistulous communication involving the urinary tract) the relative frequency of infection caused by Proteus, Pseudomonas, Klebsiella, Enterobacter spp. and by enterococci and staphylococci increases greatly. In the presence of structural abnormalities, it is also relatively common to isolate not only one but multiple organisms from the urine (6,10).

The environment in hospitals and long-term care facilities is an important determinant of the nature of the bacterial flora in urinary tract infection. Proteus, Klebsiella, Enterobacter, and Pseudomonas and staphylococci and enterococci are more often isolated from inpatients, compared with a greater occurrence of *E.coli* in an outpatient population (6,10). Anaerobic organisms are rare pathogens in urinary tract infections. Other various bacteria may on the other hand be found the urine in specific clinical settings. Fungi (particularly Candida spp.) occur in patients with indwelling catheter that are receiving antimicrobial therapy. Coagulase- negative staphylococci are a common cause of urinary tract infection in some cases. *Staphylococcus saprophyticus*, which is coagulase negative, tends to cause infection in young females who are sexually active. Coagulase-positive staphylococci most often reach the kidney from the hematogenous route, resulting in intrarenal or perinephric abscesses (6,12) (Figure 5).

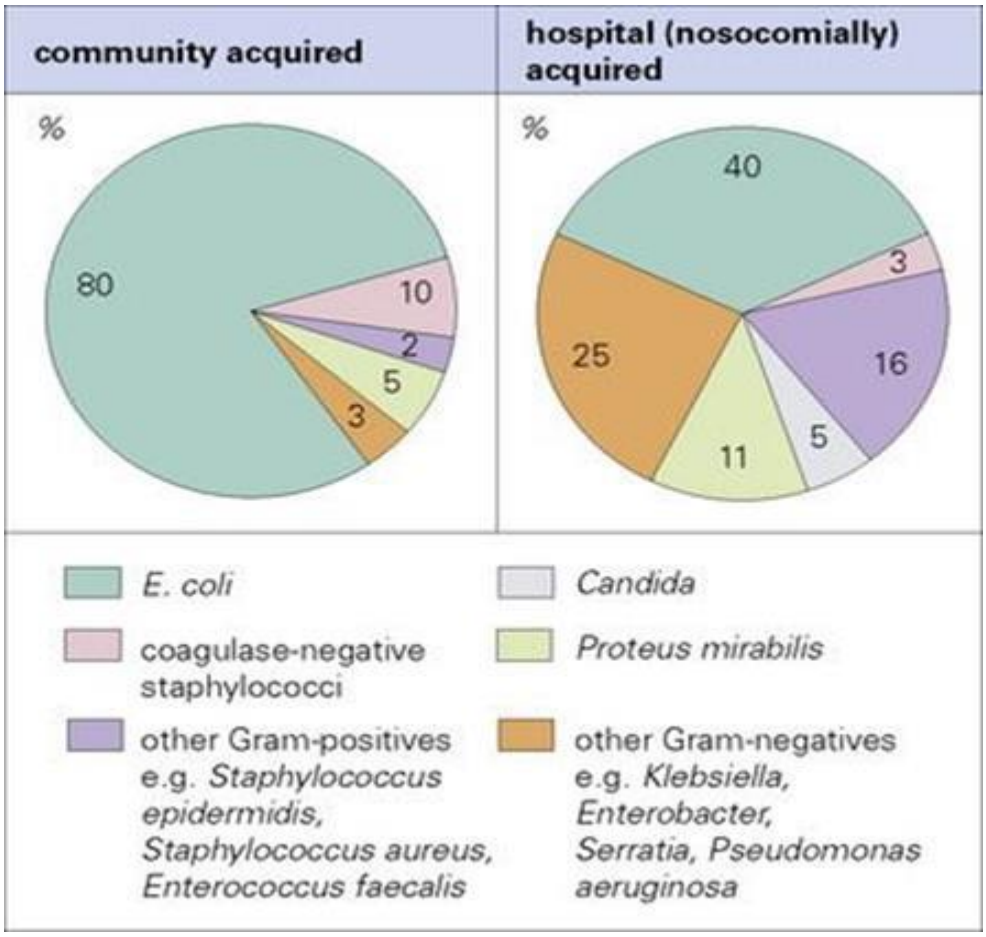

Figure 5. Common causes of UTIs in community and hospital setting
Source from http://schoolbag.info/biology/microbiology/21.html

1.5 Risk Factors

There are several predisposing factors that increase the risk of urinary tract infections including age, diabetes, benign prostatic hypertrophy, spinal cord injury, or catheterization, chronic diseases such as dementia and Alzheimer, all of these have a great impact on the etiology of UTIs. Less virulent organisms that rarely cause disease in a normal urinary tract can cause significant illness and invasive disease in an abnormal host with anatomic, metabolic or immunologic underlying disease. This results in the fact that complicated UTIs have a more diverse etiology than uncomplicated UTIs (10,11).

The etiology of UTIs in older patients depends on their general health status and whether they reside independently in the community or need long-term care. The majority of community-acquired symptomatic uncomplicated infections in elderly women are caused by *E. coli. S. saprophyticus* is a rare pathogen in this subpopulation if compared to younger sexually active women. Gram-positive organisms on the other hand are common and account for 10%

to 20% of UTIs in the older population. Polymicrobial infections are also more common in this population accounting for up to 1 in 3 patients. Another important note is that the high rate of urinary catheterization among the elderly in long-term care facilities in combination with the frequent use of systemic antibiotics, increases the risk of UTIs caused by resistant gram-negative bacteria such as *Pseudomonas aeruginosa* (10).

UTIs are considered to be one of the top concurrent illnesses with diabetes. The epidemiology between men and women with diabetes and without is quite similar. Women are at a greater risk of getting the infection in general however sexual activity and its frequency is also a factor that must be taken into account. The bacteriology and antibiotic susceptibility patterns in the general sense also do not differ from those without diabetes. On the other hand diabetic patients are more likely to have asymptomatic bacteriuria wich does not mean that there is an increased risk of symptomatic infection itself. Diabetes does however double the risk of UTI but the reason for this increase is not well understood, although bladder dysfunction, which increases with duration of diabetes and glycosuria are thought to be hypothetic mechanism (10,13).

Catheter-associated urinary tract infections remain the most common type of nosocomial infection and are a major health concern in hospitals and long term facilities. Indwelling urinary catheters are standard medical devices used to relieve urinary retention and urinary incontinence. Due to the frequent and sometimes unnecessary use of indwelling catheters during hospitalization, the risk of UTI increases by 5–8% a day of catheterization and is inevitable in long-term catheterized patients (14,15). Patients that require an indwelling catheter are as mentioned predisposed to the development of catheter-associated urinary tract infections but they are also at an increased risk for potentially pathogenic multidrug-resistant organisms. Despite the constant threat of infection from opportunistic nosocomial multiresistant strains, most cases of catheter-associated bacteriuria or the presence of bacteria in the urine are asymptomatic. The microorganisms that are often encountered in this sort of UTIs are exogenous microorganisms, such as *P.aeruginosa* or endogenous ones such as *E.coli, S.epidermidis, S. saprophyticus*, Proteus spp. and Klebsiella spp (16).

Neurogenic bladder is another risk factor that can be caused by traumatic spinal cord and brain injuries, strokes, cauda equina lesions and other diseases such as multiple sclerosis. The severity and location of the injury determine the degree and duration of the dysfunction of

the bladder. Nearly all of these patients will experience bladder dysfunction with its resulting increased risk of UTIs. The general prevalence in Europe has been stated as 15.6% of men and 17.4% of women. The microbes involved in an UTI affecting a patient with a neurogenic bladder are the same as any other patient, the specific incidence varies. The rates are: *E.coli* 60% to 65%, *P. mirabilis* 14%, *K.pneumoniae* 10%, Staphylococcus species 4%, and then other enterobacteria. There are some variations between men and women that have been reported with the predominant organism being *E.coli* in women and in men Gram-positive cocci. An important note is that, it has been identified that *E.coli* colonization does not increase the risk of symptomatic disease or deterioration of the upper urinary tract (11).

1.6 Clinical picture and complications

Accounted for in uncomplicated urinary tract infection is cystitis (infection of the bladder or lower UTI) and has the following symptoms: dysuria with or without frequency, urgency, suprapubic pain, or hematuria. Urinary frequency is the most common presenting symptom. Dysuria is also quite common with urethritis or vaginitis, but cystitis is more likely when symptoms include frequency, urgency, or hematuria and when the onset of symptoms is sudden or severe, without the presence of vaginal irritation and discharge. Those patients that are not given antibiotics, and those with antibiotic resistant organisms, complain of at least one symptom that is moderately severe or worsening and lasting for five days. Cystitis being the probable cause is greater than 50% in women with any symptoms of UTI and greater than 90% in women who have dysuria and frequency without vaginal discharge or irritation. That is the reason why additional urine analysis is not always needed in this patient group. Acute uncomplicated cystitis rarely progresses to severe disease, even if untreated (17,18).

Complicated infections are UTIs in a host, which has an increased risk to develop complications (complicated host). A complicated host is defined as one that has an increased risk for complications of the UTI, such as the following men, pregnant women, immunocompromised patients, or those who have an anatomical or functional abnormality of the urogenital tract (e.g., renal stones, urinary catheter, neurogenic bladder, diabetes, dementia spinal cord injury, renal transplant and so on). Systemic symptoms can be noticed by signs of tissue invasion, like fever, flank pain, and delirium. These UTIs can be called febrile UTI and include urosepsis, pyelonephritis, and prostatitis (17,18).

In acute pyelonephritis the typical clinical manifestations suggestive of the infection are fever (temperature >38°C) and chills, mental confusion as a sign of delirium, flank pain, costovertebral-angle tenderness, and nausea or vomiting. Symptoms may vary profusely and flank tenderness may be more intense when an obstructive disease is present. Normal kidney function can be present, but progressive destruction of the kidney may give rise to clinical manifestations of renal insufficiency (17,19).

Prostatitis is an infection that has quite a variable range of clinical signs, from a straightforward clinical entity in its acute form to a complex, debilitating condition when chronic. Patients with acute prostatitis complain of symptoms associated with lower UTI, such as frequency and dysuria. They may as well experience lower urinary-tract obstruction due to prostatic edema. On physical examination, patients may show signs of a high temperature and lower abdominal or suprapubic discomfort due to bladder infection. The rectal examination shows a tender prostate on palpation but the diagnosis can not be excluded due to a normal rectal examination (17,20). UTIs in a men are generally considered to be complicated UTIs because the prostate is often involved. However, men with a bacterial UTI can be separated into three groups. Young men with a UTI without systemic symptoms where there is no suggestive a causative factor. The UTIs in this group are considered to be uncomplicated UTIs, but are uncommon. The second group are men with a UTI and systemic symptoms or with a causative factor in their medical history or physical examination. These UTIs are considered as complicated UTIs. The systemic symptoms indicate invasion of the tissue in the prostate (acute bacterial prostatitis) or the kidney (pyelonephritis). The third group consists of men with chronic bacterial prostatitis. In these cases, it is advised to wait for the results of the culture (21,22).

The term urosepsis is commonly used to describe the sepsis syndrome caused by urinary tract infection and is considered to be a complication. The severity of sepsis mainly depends on the response of the host. The underlying UTI is almost exclusively a complicated one with involvement of parenchymatous urogenital organs (e.g., kidneys, prostate). The leading cause for developing an uroseptic shock in urological patients is urinary obstruction. It is reported that 17% of patients develop urosepsis after urological interventions. Urosepsis relates to clinical evidence of urinary tract infection plus two or more of the following: temperature, >38,0 C or <36,0 C, heart rate > 90 beats/min, respiratory rate > 20/min or PaCO <32 mm Hg, white blood count, >12,000/mm^3,< 4,000/mm^3 or >10% band forms (6,17).

Recurrent UTIs are a common health care problem and are defined as three episodes of UTI in the last 12 months or two episodes in the last 6 months. About 20 to 30% of women who have a UTI will have a recurrent UTI, which is a relapse. Relapse is a return of infection due to the same micro-organism which is often drug resistant. It is defined as the recurrence of bacteriuria with the same organism within three weeks of receiving treatment, which during treatment resulted in sterile urine. Relapse implies that there has been a failure to eradicate the infection. This most often occurs in association with renal scars, stones, cystic disease or prostatitis and in patients with chronic interstitial disease or in those who are immune compromised. Reinfection on the other hand is a recurring infection due to a different microorganism that is usually drug susceptible. Most recurring episodes of cysto-uretheritis are due to reinfections that are much more common than relapses and accounts for about 80% of recurrent infections. Unlike relapse, reinfection does not mean failure to eradicate infection from urinary tract but is due to recolonization of the system (8,23).

1.7 Diagnosis

The initial step in the diagnosis of UTIs is to obtain a thorough medical history and conduct a thorough physical examination in order to distinguish those patients with infection and to identify predisposing risk factors defining a complicated UTI.

The diagnosis of acute uncomplicated cystitis can be made with high probability based on a focused history of lower urinary tract symptoms (dysuria, frequency and urgency) in a patient who has no risk factors for complicated UTI. Urine dipstick analysis, as opposed to urinary microscopy, is a reasonable alternative to urine culture to diagnose acute uncomplicated cystitis. Urine cultures are recommended for patients with risk factors for complicated UTIs.

In a microscopic examination of urine, in a centrifuged sediment, patients with significant bacteriuria almost always show bacilli in the urine, whereas only a small amount of patients with less than 10^5 colony forming units per ml show bacteria. In significant bacteriuria about 60-85% of patients have 10 or more white blood cells per high power field in mid-stream urine. When it comes to pyuria 95 % of patients have some form of genitourinary tract infection; although, pyuria cannot distinguish between a bacterial UTI and an acute urethral syndrome. Simple gram-stained smears can be helpful in specifying the morphology and stain characteristics which can aid in identifying the likely pathogen and in targeting empiric therapy.

Urine culture is the only certain way to establish diagnosis of UTI from simple cystitis to complicated pyelonephritis with sepsis.

Imaging should be considered if urinary tract infection is slow to resolve, if there is relapse or if there are risk factors for papillary necrosis. It should be done 3-6 weeks after cure of acute infection to identify abnormalities predisposing to infection or renal damage or which may affect management. It is rarely carried out in the acute phase, particularly where there is severe loin pain. It is important to recognize that abnormalities will be found in less than 5 % of unselected cases. Patients who have severe loin pain or whose infection does not settle on treatment should have US and plain X-ray to exclude pyelonephrosis, intrarenal or perinephric sepsis or calculi. CT may be undertaken if no abnormality is seen on US in such patients. There is no indication for imaging, in women, following a single or infrequent infection. Recurrent attacks more often than 2 per 6 months should be investigated by ultrasound and plain xray, since this is the imaging of choice in these cases. In men, UTI is much less common than in women, and imaging is indicated after the first documented bacteriuria to exclude predisposing factors especially impaired bladder emptying. USG and plain film are the best first choice (5,24,25).

1.8. Treatment

The choice of treatment for UTIs depends on whether it is uncomplicated or complicated. The antimicrobial agents most commonly used to treat uncomplicated urinary tract infections include the combination drug trimethoprim and sulfamethoxazole, trimethoprim, β-lactams, fluoroquinolones, nitrofurantoin, and fosfomycin tromethamine. These agents are used primarily because of their tolerability, spectrum of activity against suspected uropathogens, and favorable concentration of the antimicrobial agent in the urine rather than serum levels. All the antimicrobial agents approved for the treatment of urinary tract infections achieve inhibitory urinary concentrations that significantly exceed serum levels. Also, agents such as trimethoprim-sulfamethoxazole or the fluoroquinolones that eradicate aerobic gram-negative flora but have little effect on the vaginal and fecal anaerobic flora seem to provide the best long-term cures for uncomplicated urinary tract infections (26,27). Due to the fact that most uncomplicated urinary tract infections are treated empirically, it is important for clinicians to be aware of the resistance patterns of uropathogens in their own community to ensure that the most appropriate antimicrobial agent is used. The emergence of resistant uropathogens has had a tremendous effect on empiric therapy in the last years. The most

dramatic increase in resistance in the past few years has been to trimethoprim-sulfamethoxazole. Another increase in resistance has been of *E.coli* to β-lactams such as ampicillin and first-generation cephalosporins which was 34% and 28%, respectively (27,28). Trimethoprim-sulfamethoxazole should be used as first-line therapy because of its low cost and efficacy for uncomplicated urinary tract infections in women unless the prevalence of resistance to these agents among uropathogens in the community is greater than 10% to 20%. The fluoroquinolones are more expensive, broader in spectrum, and therefore, should be reserved for communities with rates of resistance to trimethoprim of greater than 10% to 20% or in patients who either cannot tolerate trimethoprim-sulfamethoxazole or have recurrent urinary tract infections. Other options include a 7-day course of nitrofurantoin or a single dose of fosfomycin. The use of first-generation cephalosporins or aminopenicillins is generally not recommended because of high levels of resistance and recurrence. Although resistance to the third-generation cephalosporins is lower than to the first generation, these agents are considered third-line agents because of their cost and efficacy (29,30).

The main goal of managing complicated UTIs is optimal administration of appropriate antimicrobial agent and correction of any underlying genitourinary abnormalities. Optimal administration includes a treatment given on time, appropriate selection and dosing of antimicrobial agents to which the potential pathogen is susceptible to. In order to select an appropriate empiric therapy, clinicians must be well aware of the institution-specific resistance patterns. Once culture and sensitivity reports are available, therapy should be adapted accordingly. In addition, therapy selection is influenced by host-specific factors such as, previous anti-infective exposure, severity of signs and symptoms, allergy history, and organ dysfunction (31,32).

Antimicrobial resistance is commonly encountered in complicated UTIs for many reasons. These patients have recurrent infections frequently and receive repeated courses of antimicrobial therapy. In addition, patients may acquire infection nosocomially through instrumentation (catheters) and organisms acquired this way are more likely to be resistant than those acquired in the community (33,34). Antimicrobial resistance is a concern for gram-negative organisms since these represent the dominant etiology of complicated UTIs. There is a global indication of increased rates of resistance in uropathogens in general. Although the specific concerns relate to multi-drug resistance, as there is an increased incidence of AmpC β-lactamases and extended-spectrum β-lactamase (ESBL)–producing organisms (35).

E.coli is becoming increasingly resistant to first-line antimicrobial therapy. Resistance of *E.coli* to trimethoprim-sulfamethoxazole (TMP-SMX) and fluoroquinolones is 21% to 28% and 7% to 40%, respectively(36,37). The greatest risk factors for the increased resistance of TMP-SMX and fluoroquinolone in *E.coli* are high levels of TMP-SMX and fluoroquinolone being prescribed in the health care setting and residency in long-term care facilities (38,39) On the other hand, the resistance rates of *E.coli* to carbapenems, cephalosporins, and piperacillin/tazobactam remained low and stable (28). Carbapenems are considered the drugs of choice for the treatment of severe infections due to ESBL-producing Enterobacteriaceae. Other agents that could be useful in the treatments of of ESBL-associated UTIs include fosfomycin, nitrofurantoin, tigecycline, polymyxins, and aminoglycosides depending on susceptibility. Fosfomycin and nitrofurantoin should only be used for the treatment of lower UTIs and are contraindicated in patients with pyelonephritis (40). Aminoglycosides can be used to manage UTIs caused by ESBL-producing bacteria despite the associated toxicity but there has been a recent increase with the worldwide emergence of resistant *E.coli* in the community setting (28,41). AmpC β-lactamases are clinically important cephalosporinases encoded on the chromosome of many Enterobacteriaceae and a few other organisms where they mediate resistance to cefazolin, cefotaxime, ceftazidime, and ceftriaxone, most penicillins, and β-lactamase inhibitor/β-lactam combinations. They can appear in *E.coli, K.pneumoniae,* and *P. mirabilis*. AmpC β-lactamase–producing *E.coli* is an emerging community pathogen that commonly causes UTIs in older women. Carbapenems are the drug of choice for serious infections caused by these organisms, but if the isolate is susceptible, fluoroquinolones are considered to be a fitting option for the treatment of non–life-threatening UTIs caused by AmpC β-lactamase–producing organisms (42).

Carbapenems are considered optimal choices for mixed infections as they exhibit a broad spectrum of activity versus Gram-negative and Gram-positive organisms, including ESBL- and AmpC-producing organism (43).

High-dose fluoroquinolones such as levofloxacin might be successful in treatment of mild UTI with fluoroquinolone-resistant, Gram-negative uropathogen. Although it should be taken into consideration that fluoroquinolones should not be used as empiric treatment of complicated UTIs, in patients with recent use of fluoroquinolones, recurrent UTIs, and recent hospitalization due to the emergence of fluoroquinolone resistant uropathogens (28,44).

Traditionally, an aminoglycoside alone or in combination with a β-lactam has been considered a first-line option for the management of complicated UTIs and they are frequently recommended as a therapeutic option. The downside of these antibiotics is that they continue to be associated with an increased risk of nephrotoxicity and ototoxicity. Therefore they should be reserved for the treatment of complicated UTIs where other safe and effective antimicrobial agents are not appropriate (28,45).

2. OBJECTIVES

The aims of the study were

1. To analyze the predisposing factors in a patient with an infection in the urinary tract system

2. To analyze the most common causative pathogens of urinary tract infections.

3. To analyze the antibiotic sensitivity of the most common causative pathogens of urinary tract infections, and to this way conclude the proper choice of initial empirical antibiotic therapy for all our patients.

3. MATERIALS AND METHODS

3.1 Study population

In this study 175 patients were included with the diagnosis cystitis, pyelonephritis and prostatitis, with no proven bacteremia, which were treated at the Clinic of Infectology at the University Hospital of Split, in the period of years 2016-2017. All patients were diagnosed on the basis of clinical evaluation and laboratory diagnostics.

3.2. Study Design

This study was conducted as an observational retrospective study.

3.3. Method of collecting and analyzing data

Medical data of eligible patients was retrieved from a written protocol at the Clinic of Infectology at the University Hospital of Split and collected by reviewing the history of medical files from the archive. The collected data was then inserted in Microsoft Office packages in Microsoft Excel program.

3.4 Research Method

By using the medical history and discharge papers of our patients, the occurrence of urinary tract infections in certain age groups, in both genders were analyzed. On the basis of the collected data about comorbidities possible risk factors were analyzed together with the amount of patients with the possibility of more than one comorbidity. With the use of microbiological test results in urine cultures the etiology of urinary tract infections and their sensitivity to the main groups of antibiotics were analyzed.

4. RESULTS

In Table 1. the distribution of patients by age and gender is shown. The mean age of the patients was 60.6 years. The mean age for females was 57.7 years. The mean age for males was 65.5 years. The largest number of patients (27.4%) were in the age group from 80 years and on. Most of the patients were women (61.1%).

Table 1. Distribution of patients with urinary tract infection (UTI) according to age and sex

Age (years)	**Female** **Number (%)**	**Male** **Number (%)**	**Total** **Number (%)**
≤19	3 (1.7)	2 (1.1)	5 (2.9)
20-39	33 (18.9)	3 (1.7)	36 (20.7)
40-59	17 (9.7)	17 (9.7)	34 (19.4)
60-69	12 (6.9)	12 (6.9)	24 (13.7)
70-79	18 (10.3)	10 (5.7)	28 (16.0)
≥80	24 (13.7)	24 (13.7)	48 (27.4)
Total	**107 (61.1)**	**68 (38.9)**	**175(100.0)**

Table 2. shows the distribution of clinical diagnosis among the patients. The largest number of patients, 85.1% had pyelonephritis and only 2.3% had cystitis as a clinical diagnosis.

Table 2. Clinical diagnosis of patients with UTI

Diagnosis	**Number (%)**
Pyelonephritis	149 (85.1)
Cystitis	4 (2.3)
Prostatitis/prostatocystitis	22 (12.6)
Total	**175 (100.0)**

Table 3. presents the distribution of patients with the number of predisposing conditions. Most patients had no known predisposing condition, 38.3% had 2 or less than 2 predisposing conditions. Only 10.9% had 3 or more predisposing conditions. All together there were 86 patients (67+19) with some kind of know predisposing factor.

Table 3. Distribution of patients with UTIs according to the number of predisposing conditions

Number of predispositions	**Number of patients (%)**
No	89 (50.9)
≤ 2	67 (38.3)
≥ 3	19 (10.9)
Total	**175 (100.0)**

Table 4. gives a representation of the predisposing factors related to urinary tract infections. Some patients had more then one predisposing condition which is seen in Table 3. The most common predisposing factor is diabetes mellitus with 14.9%, followed by neurological urine incontinence/retention with 13.7%. Abdominal malignancies affecting the urinary tract and obstructive uropathies were the predisposing conditions with the lowest number of patients, 2.3%.

Table 4. Predisposing conditions in patients with UTIs

Condition	**Number of patients (%)**
Urinary catheter	13 (7.4)
Neurological urine incontinence/ retention	24 (13.7)
Urinary tract stones	8 (4.6)
Benign prostatic hypertrophy	8 (4.6)
Urinary tract malignancy	9 (5.1)
Other abdominal malignancies affecting urinary tract	4 (2.3)
Other obstructive uropathies (hydronephrosis)	4 (2.3)
Diabetes mellitus	26 (14.9)
Other chronic diseases	9 (5.1)

Table 5. shows the etiology of urinary tract infections acquired from urine culture. The most common isolate by far was *E.coli* with 62.8%, followed by *P.aureginosa* with 10.2%. At third place was *P.mirabilis* with 8.2%.

Table 5. Etiology of UTI

Agent	**Urine culture [number (%)]**
E. coli	123 (62.8)
Klebsiella	11 (5.6)
P. mirabilis	16 (8.2)
P.aureginosa	20 (10.2)
M.morgagnii	6 (3.1)
Citrobacter	4 (2.0)
E.faecalis	7 (3.6)
E.faecium	1 (0.5)
S.saprophyticus	1 (0.5)
S.aureus	1 (0.5)
S.aerogenes	1 (0.5)
A.baumanii	4 (2)
E.cloacae	1 (0.5)
Total	**196(100.0)**

Table 6. shows the sensitivity and resistance of *E.coli* to different antibiotics. The resistance was highest towards ampicillin 48.0%. Trimetroprim-sulfamethoxazole was the second antibiotic in exhibiting resistance in *E.coli* with 29.3%, followed by fluoroquinolones. Amoxicillin-clavulanic acid showed low resistance, 7.0% and high sensitivity, 93.5%. No isolates of *E.coli* were found to be resistant to Carbapenems.

Table 6. Antibiotic sensitivity of *Esherichia coli* in patients with UTI

Antibiotic	Sensitive (Number (%))	Resistant (Number (%))	Total Number
Ampicillin	64 (52.0)	59 (48.0)	123
Amoxicillin-clavulanic acid	115 (93.5)	8 (7.0)	123
Carbepenem	123 (100.0)	0	123
Cephalosporins 1 and 2nd generation	102 (83.0)	21 (17.1)	123
Cephalosporin 3	105 (85.4)	18 (14.6)	123
Trimetroprim-sulfamethoxazole	87 (70.7)	36 (29.3)	123
Fluoroquinolones	95 (77.2)	28 (22.8)	123
Aminoglycosides	111 (90.2)	12 (10.1)	123

Table 7. shows the distribution of different pathogens and their resistance to antibiotics. Only 3 *A.baumanii*, 1 *P.mirabilis* and 1 *P.aureginosa* isolates were found to be resistant against Carbepenem. The most occurring resistance was in *E.coli* where 35 isolates were Trimetoprim-sulphametoxazole resistant. The second most occurring resistance was also found in *E.coli* where 26 isolates were resistant to quionolones. Klebsiella species showed resistance to several antibiotics in the 11 isolates, where 5 isolates were ESBL+ and 5 were quinolone resistant.

. **Table 7.** Distribution of causative organisms of UTI according to their antibiotic resistance

Organism	No of isolates	Antibiotic resistant isolates [number (%)]				
		Amox-clav R*	ESBL+**	CR$	Quionolone R	TMP/SMX# R
E. coli	124	7 (5,6)	20 (16,1)	0	26 (21,0)	35 (28,2)
Klebsiella	11	3 (27,3)	5 (45,5)	0	5 (45,5)	4 (36,4)
P.mirabilis	16	0	0	1 (6,3)	7 (43,8)	3 (18,8)
P.aureginosa	20	na+	3++ (15)	1(5)	5 (25)	na
M.morgagnii	6	5 (83,3)	0	0	0	4 (66,7)
Citrobacter	4	2 (50)	0	0	0	0
Enterococcus	7	1 (14,3)	na	Na	3	0
A.baumanii	4	0	0	3 (75)	2	0

Legend
*__Amox-clav R__: amoxicillin-clavulanate resistant; **__ESBL+__: extended β-lactamase positive; $__CR-__ carbapenem resistant; #__TMP/SMX R__:Trimetoprim-sulphametoxazole resistant; +__na__: not available; __3__++: 3 *P.aeruginosa* isolates were resistant to cefatizidim and piperacillin-tazobactam

5. DISCUSSION

Urinary tract infections are among the most commonly experienced infections by humans after respiratory and gastro-intestinal infections that can occur at any age (5). However there is a difference in the prevalence between men and women. In our patients there was a significantly greater number of women (61.1%) then men (38.9%) and this difference is most prominent up until the age of 39. The greatest difference between the two genders was in the age group 20-39 where 33 women and 3 men had the infection. This great difference between sexually active women and men is related to a set of other factors, including the larger distance between the anus (the usual source of uropathogens) and the urethra, the dry environment around the male urethra and the antibacterial activity of prostatic fluid. The female urethra is also shorter than the male one and is in proximity to the vulvar and perianal areas making contamination likely (8–10).

As the age increases the incidence of urinary tract infection in men also increases. In our patients the incidence is especially high in men affected by the infection from 80 years and onward, more then 1/3 of the total amount of male patients reside in this age group. This increase in infection rate as men age is due to acquired structural and functional abnormalities of the urinary tract that impair normal voiding; the most common being, benign prostatic hyperplasia, which can cause urinary tract infection owing to obstruction and turbulent urine flow (46-48). When it comes to the fact, that the number of men and women in the higher age groups is equal in number, this is not supported by scientific literature. It still states that women are the most commonly affected gender even in the older age groups. Although a greater number of patients, in the higher age groups, would have been needed in our study to conclude anything. However literature also states that accurately measuring the incidence of urinary tract infections in the elderly is difficult since criteria used for diagnosis are not consistent across epidemiologic studies. In our study the highest number of patients were in the age group from 80 years and on, which correlates with the general fact that incidence of infection increases with age (46).

In our research patients without positive hemoculture were documented. Amongst those patients 85.1% had pyelonephritis as a diagnosis, 12.6% patients had prostatitis/prostatocystitis and the lowest number of patients had cystitis 2.3%. This sort of division of clinical symptoms was to be expected as pyelonephritis is clinically more severe and easier to detect than acute prostatitis. While patients with cystitis are rarely hospitalized and if so it occurs in situations where parenteral antibiotic treatment is the only choice of treatment (17,20).

There are several predisposing factors that increase the risk of urinary tract infections including age, diabetes, benign prostatic hypertrophy, spinal cord injury, catheterization, chronic diseases and all of these have a great impact on the etiology of urinary tract infections (10,11). In our patients 50.9 % had predispositions known to us, 38.3 % had 2 or less predispositions and 10.9 % had 3 or more predispositions. All together 89 patients had no predispositions while 86 patients had some kind of known predispositions. This does not exclude the fact that there is an increased risk of disease with these factors. Articles do state that with age patients have more of the above mentioned risk factors such as catheter, diabetes, urinary disturbances and so on (11,46). What would have been interesting to add in our study, which is also a limitation is, the relation of age and predispositions. To see how many patients in the different age groups, between the two genders, had predispositions that increase the risk of urinary tract infections.

As expected and in accordance to literature different kinds of disruption of the normal urinary flow, when combined, are the most common predisposing factors of urinary tract infections. Our study had 24 patients with neurologic factors, 13 with urinary catheters, 8 with urinary tract stones, 8 with benign prostatic hypertrophy and 4 with obstructive uropathies, this results in a combination of 57 patients with disrupted urinary flow. Among our patients, neurologic factors (immobility, Alzheimer's, dementia, multiple sclerosis with resulting urinary incontinence/retention) were the second most common predisposition for infection (10,11). The most common predisposing factor in our study was diabetes mellitus with 26 patients in total. There is a known increased risk of developing urinary tract infections with diabetes mellitus. It is actually considered to be one of top ten risk factors for urinary tract infections and has quite an increase in incidence with age (10,13). The rest of the predisposing factors in our study cause anatomic, metabolic or immunologic disease which all give an increased risk (10,11). All of these patients with predisposing conditions are considered to have complicated urinary tract infections (17,18). The predisposing factors mentioned increase with age and less virulent organisms, that rarely cause disease in a normal urinary tract, can cause significant illness and invasive disease with one of the mentioned predisposing factors (46). This results in the fact that complicated UTIs have a more severe disease outcome than uncomplicated UTIs (10,11). The limitation in our study in this section was the lack of the relation of age and predispositions, to see what specific predispositions occurred the most in what age groups, between the two genders, with a more extensive number of patients.

Amongst our patients *E.coli* (62.8%) was by far the most common cause of urinary tract infections, in second place was *P.aureginosa* (10.2%) followed by *P.mirabilis* (8.2%), Klebsiella (5.6%) and the remaining isolates were even fewer in number. What is of great importance to notice is that in our study we did not differentiate between community acquired and hospital acquired pathogens. In literature, in a community acquired setting, *Escherichia coli* accounts for 75% to 90% of cases, *Klebsiella* species and *Proteus mirabilis*, account for the remaining 5% to 10% (27). When looking at literature for hospital acquired infections the most commonly isolated pathogens are *E. coli* (35.3%), Enterococcus sp. (15.2%), Klebsiella sp. (9.8%) and *Pseudomonas aeruginosa* (5.4%) (49-51). *E.coli* is more prevalent in a community acquired setting while other pathogens, such as *P.aureginosa, P.mirabilis* and Klebsiella species are more prevalent in a hospital acquired setting. When comparing our study to the percentages of community acquired isolates, we have a lower number of *E.coli* isolates. Which could be explained by the fact that we had some hospital acquired or recurrent infections and a higher number of bacteria (*P.aureginosa, P.mirabilis*, Klebsiella species) that are more prevalent in hospital infections.

There has been a great increase in resistance among Enterobacteriacae around the world. These bacteria, including *E.coli*, have acquired a high prevalence of resistance against penicillins such as ampicillin even when community acquired infections are considered. The resistance of *E. coli* to b-lactams, such as ampicillin, and the first-generation cephalosporins has continued to increase in the past decade and now approaches 40% in most studies (28,27). In an extensive susceptibility study in Croatia, the resistance of *E.coli* to ampicillin is even higher accounting for 50% in 2016 (49). This correlates with our study, where 48.0% of the *E.coli* isolates where resistant to ampicillin. Logically this excludes ampicillin from any kind of first choice for empirical treatment of urinary tract infections. The percentage of resistance might have been somewhat lower in exclusively community acquired isolates, which was not studied in our patients. This would have still not rendered ampicillin for empirical use. The resistance of *E.coli* isolates against amoxicillin-clavulanic acid was only 7.3%, which closely correlates with the resistance in Croatia (49). Therefore amoxicillin-clavulanic acid is an appropriate first choice of empirical treatment for community acquired urinary tract infections. If it would be equally appropriate for hospital acquired infections was not studied in our patients. Another antibiotic to which *E.coli* has a great increase in resistance is trimethoprim-sulphametoxazole, especially in hospital settings. In literature the resistance of *E.coli* to trimethoprim-sulfamethoxazole is 21% to 28% (36,37). In studies done in Croatia the resistance

against this antibiotic is at 27% (49). Our patients had a resistance of 29.3% which correlates well with the previous studies mentioned above. This however excludes trimethoprim-sulfamethoxazole as a first choice antibiotic for empirical treatment and it is therefore only an option once susceptibility to it has been confirmed.

What was unexpected was the number of resistant isolates against third-generation cephalsporines which was 14.6%.This makes third generation cephalsporins less reliable then amoxicillin-clavulanic acid as a treatment option. Although no conclusion can be made since there is a lack of differentiation between community and hospital acquired infection in our study. According to a Croatian study, the resistance is 6-9% to these antibiotics (49). In general in the EU/EEA the mean percentage of resistance to third-generation cephalosporins increased significantly from 9.5% in 2010 to 12.6% in 2013 (50).

A Croatian susceptibility study showed a resistance of 19% in *E.coli* to fluoroquinolones (49). The EU/EEA population-weighted mean percentage for fluoroquinolone resistance was 22.4 % in 2014(51). In our study 22.8% of our isolates were resistant to this antibiotic which would mean that it would not be considered as a good first choice for treatment. Again it is important to note that this number could be lower in infections acquired in community. This antibiotic is considered to be a good first choice treatment in uncomplicated urinary tract infections, according to literature (26,27).

When the overall distribution of the causative organisms of UTI and their antibiotic resistance in our study are evaluated, *E.coli* is the dominant isolate. Amoxicillin-clavulanic acid is a reliable first line choice of empirical antibiotic treatment. The same seems to be correct for the treatment of *P.mirabilis* and to some extent for *K.pneumoniae*. However the low number of these two isolates makes it impossible to conclude anything. To be able to do that for the isolates with a low number, a more extensive study would be needed with greater number of patients and a differentiation between community and hospital acquired infection. But as it seems amoxicillin-clavulanic acid would be a reliable choice anyway. When it comes to Carbepenems, except for the expected resistance found in *A.baumanii*, there is basically no resistance to this antibiotic. Even though our study was limited by the lack of data to distinguish between community and hospital acquired infection, it is still obvious that carbepenems are very reliable in the choice of empirical treatment for hospital acquired urinary tract infections. This observation is concluded by scientific literature (42,43).

6. CONCLUSION

1. Half of our patients did not have any predisposing conditions for UTIs. The most common predisposing factors in our patients were diabetes mellitus, variety of neurological conditions that are associated with urin incontinence or retention, and long term urinary catheters. High age, especially above 80 years, is connected with an increased incidence of UTIs.

2. In our patients, with a number over 60% the most common pathogen was *E.coli*, far behind it in second place was *P.aureginosa* with only 10.2%, and the rest of the bacteria were in a margin from 0.5-8.2%.

3. Over 90% of *E.coli* isolates were sensitive to amoxicillin-clavulanic acid which makes this antibiotic a reliable first choice as an empirical treatment for community acquired UTIs. Trimethoprim-sulfamethoxazole, fluoroquinolone and to a certain degree cephalosporins should not be used before the antibiotic susceptibility of the pathogen is known. Carbapenems are reliable first choice antibiotics, but they should be reserved for patients with recurrent or hospital acquired UTIs.

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8. SUMMARY

OBJECTIVES: confirm the predisposing conditions, the most common causative pathogen and their sensitivity to different antibiotics in patients with urinary tract infections (UTIs).

MATERIAL AND METHODS: the study included 175 patients with the diagnosis cystitis, pyelonephritis and prostatitis, with no proven bacteremia, which were treated at the Clinic of Infectology at the University Hospital of Split, in the period of years 2016-2017. All patients were diagnosed on the basis of clinical evaluation and laboratory diagnostics. Study was conducted as an observational retrospective study. Medical data were collected by reviewing the history of medical files from the archive of at the Clinic of Infectology.

RESULTS: the largest number of patients (27.4%) were in the age group from 80 years and on. Most of the patients in the study were women (61.1%). Almost half of the patients (48.9%) had one or more predisposing conditions for UTIs. The most frequent predispositions were diabetes mellitus (14.9%), variety of neurological conditions that are associated with urin incontinence or retention (13.7%), and long term urinary catheters (7.4%). *E.coli* (62.8%) was by far the most common cause of urinary tract infections, in second place was *P.aureginosa* (10.2%) followed by *P.mirabilis* (8.2%), Klebsiella (5.6%). Almost half (48.0%) of the *E.coli* isolates where resistant to ampicillin, and only 7.3% were resistant to amoxicillin-clavulanate, while resistence to trimetoprim-sulphametoxazole and fluroquinolones was 29.3% and 22.8%, respectively. Almost all bacteria, with exception of *A.baumanii*, causing UTIs in our patients were sensitive do carbapenems.

CONCLUSIONS: Diabetes mellitus was the most common predisposing factor in our patients. With a number over 60% the most common pathogen was *E.coli*, far behind it in second place was *P.aureginosa* with only 10.2%. Over 90% of *E.coli* isolates were sensitive to amoxicillin-clavulanic acid which makes this antibiotic a reliable first choice as an empirical treatment for community acquired UTIs.Trimethoprim-sulfamethoxazole, fluoroquinolone and to a certain degree cephalosporins should not be used before the antibiotic susceptibility of the pathogen is known. Carbapenems are a reliable first choice of antibiotics.

9. CROATIAN SUMMARY

Naslov: Infekcije mokraćnog sustava liječene na Klinici za infektologiju Kliničkog bolničkog centra Split u razdoblju od 2016.-2017. godine: epidemiološke, kliničke i mikrobiološke osobine.

Ciljevi: utvrditi predispozicijske čimbenike, najčešće uzročnike i njihovu osjetljivost na antibiotike u bolesnika s infekcijama mokraćnog sustava (IMS).

Materijali i metode: Studija je obuhvatila 175 bolesnika s dijagnozom cistitisa, pijelonefitisa i prostatitisa bez dokazane bakterijemije koji su liječeni na Klinici za infektologiju kliničkog bolničkog centra Split u razdoblju od 2016.-2017.godine. Svim bolesnicima je dijagnoza postavljena temeljem kliničke procjene i laboratorijske dijagnostike. Medicinski podaci su prikupljeni pregledom povijesti bolesti iz arhive Klinike za infektologiju.

Rezultati: Najviše bolesnika (27,4%) bio je u dobnoj skupni od 80 i više godina. Većina bolesnika bile su žene (61,1%). Gotovo polovica naših bolesnika (48,9%) imala je jedan ili više predispozicijskih čimbenika za infekciju mokraćnog sustava. Najzastupljenije predispozicije su bile diabetes mellitus (14,9%), različita neurološka stanja koja su povezana s inkontinencijom ili retencijom urina (13,7%) i trajni urinski kateter (7,4%). *E.coli* bila je daleko najčešći uzročnik IMS (62,8%), na drugom mjestu *P.aureginosa* (10,2%), a potom slijede *P.mirabilis* (8,2%) i Klebsiella (5,6%). Gotovo polovica izoliranih *E.coli* (48,0%) bilo je rezistentno na ampicilin, a samo 7,3% ih je bilo rezistentno na amoksicilin-klavulanat, dok ih je na trimetoprim-sulfametoksazol i flurokinolone bilo rezistetno 29,3% , odnosno 22,8%. Gotovo sve bakterije, s izuzetkom *A. bauumanii*, koje su uzrokovale IMS u naših bolesnka bile su osjetljive na karbapeneme.

Zaključci: Dijabetes melitus je najčešći predispozcijski faktor IMSa u naših bolesnika. S udjelom od preko 60% najčešći uzročnik bio je *E.coli* , a daleko iza nje na drugom mjestu je *P.aeruginosa* s tek 10,2% . Preko 90% izolata *E.coli* bilo je osjetljivo na amksicilin-klavulanat što čini ovaj antibiotik pouzdanih prvim izborom za empirijsko liječenje vanbolnički stečenih IMSa. Trimetoprim-sulfametoxazol, fluorokionolone, pa u određenom opsegu i cefalosporine ne bi trebalo primjenjivati prije nego je poznata antibiotska osjetljivost uzročnika. Karbapenemi su pouzdani antibiotici prvog izbora.

10. CURRICULUM VITAE

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