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UNIVERSITY OF SPLIT
SCHOOL OF MEDICINE

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ETIOLOGY AND ANTIBIOTIC SENSITIVITY OF URINARY TRACT INFECTIONS IN ELDERLY PATIENTS TREATED DURING THE YEAR 2018 IN CLINIC FOR INFECTOLOGY, UNIVERSITY HOSPITAL SPLIT

Diploma thesis

Academic year:
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Split, July 2019

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Table of contents

First of all, I would like to express my sincere gratitude to my mentor Assoc. Prof. Ivo Ivić MD, PhD for the continuous help and guidance throughout this thesis. My gratitude also goes to the Department of Infectology for giving me the opportunity to collect data at all hours and being understanding and supportive at all times.

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1. INTRODUCTION

1.1. Urinary tract anatomy

The Urinary Tract is a contiguous hollow organ system comprised of, from proximal to distal, the renal papillae, renal pelvis, ureters, bladder and urethra. Each component has its distinct anatomic features and critical function, which is to collect, transport, store and expel urine. Constant urine flow in the upper and intermittent elimination from the lower urinary tract ensures the cleansing of the urinary tract and represent one of many host defensive mechanisms that prevent colonization of microbes that have gained access to the urinary system (1,2).

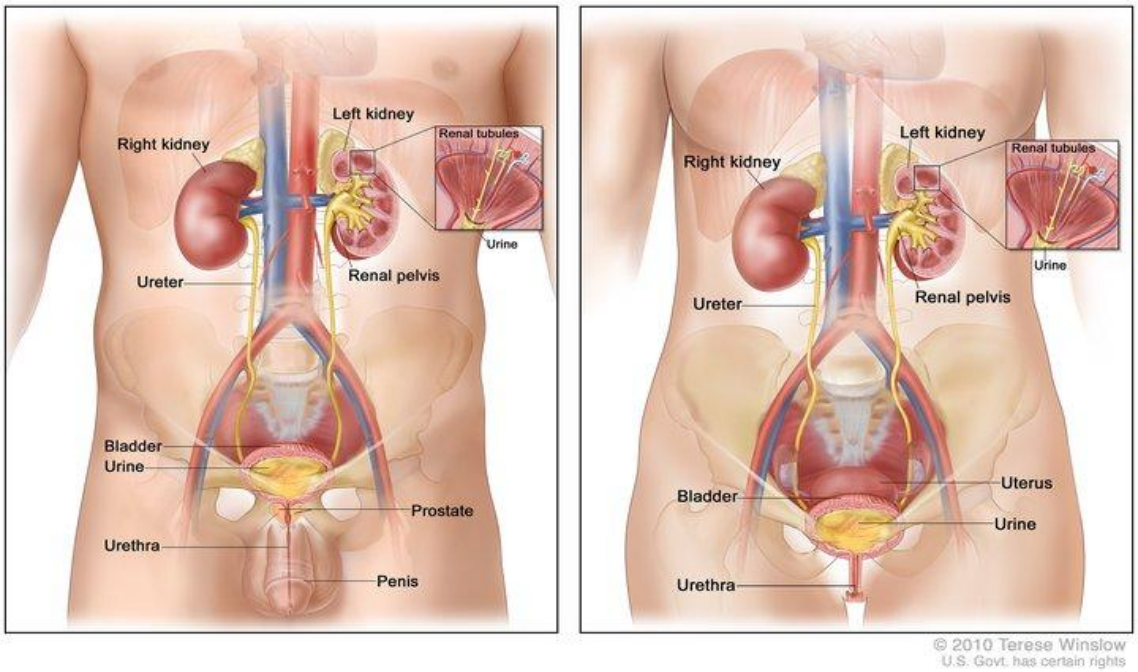

Figure 1. Anatomy of the male and female urinary system from left to right
Source taken from http://anatomymedicalook.com/anatomy-of-a-womens-urinay-system/anatomy-ofa-womens-urinay-system-anatomy-of-a-womens-urinay-system-kidney-location-in-women/

The anatomical differences between male and female anatomy of the lower urinary tract plays a crucial role in the pathogenesis and epidemiology of urinary tract infections.

In males, the bladder lies between rectum and pubic symphysis. The base of the bladder rests on the endopelvic fascia and pelvic floor musculature, thus fastening the bladder neck behind the symphysis. A smooth muscle layer surrounding the bladder neck forms an involuntary internal-urethral sphincter. In females, the bladder is placed between rectum and uterus/vagina. The base of the bladder and urethra rest on the anterior wall of the vagina and the internal-urethra sphincter is not as well developed as in men (1,3).

Urethral length in males ranges between 13 and 20 cm and is divided into prostatic, membranous and penile portions. Female urethra is remarkably shorter with 3.8 to 5.1cm in length and passes obliquely from the bladder neck to external-urethral meatus along the anterior vaginal wall. The distal two-third are surrounded by slow-twitch striated muscles forming the external-urethral sphincter.

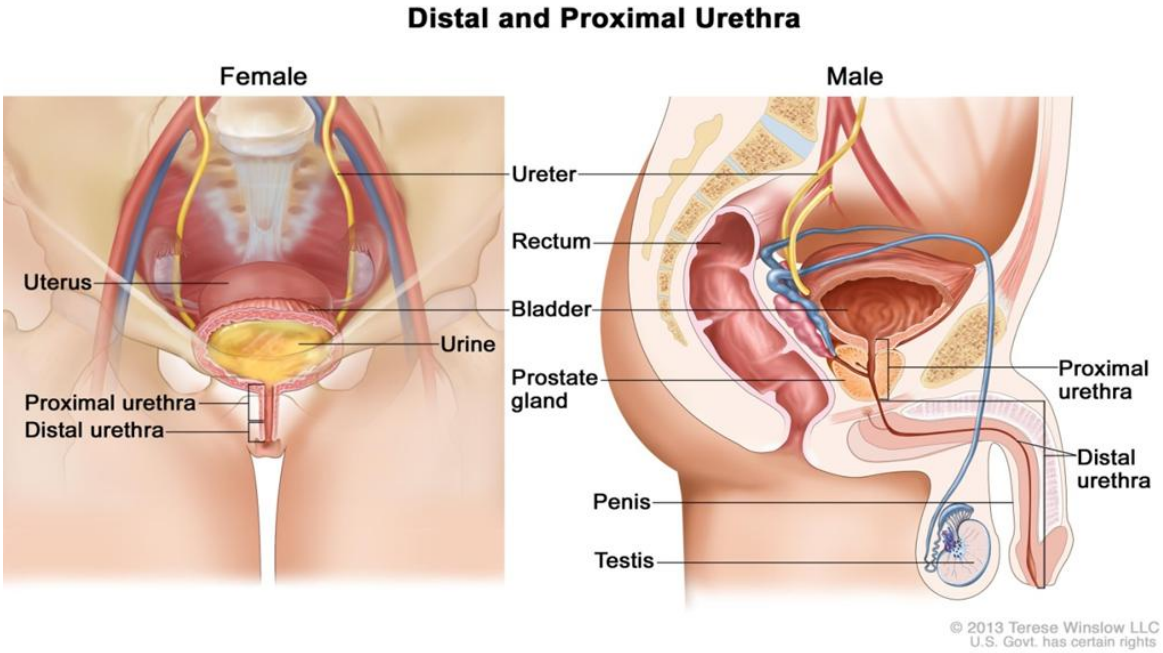

Figure 2. Anatomy of the female and male urinary tract with focus on urethra
Source taken from http://anatomymedicalook.com/anatomy-of-a-womens-urinary-system/anatomy-of-a-womens-urinary-system-female-urinary-tract-diagram-female-reproductive-and-urinary/

Short urethral length and close proximity to the vagina play an important role in urinary tract infection (UTI) pathogenesis. The warm, moist, vulvar and perianal areas make contamination likely and support the importance of ascending route of infection and higher prevalence of UTIs in women. Causative organisms in women colonize vaginal introitus and perurethral area typically before resulting in infection (1).

1.2. Urinary tract infections and etiology

Urinary tract infections (UTI) are the most common infections found in outpatient practice and are especially common in elderly patient population. Improper diagnosis and

globally growing antibiotic resistance of pathogens, particularly against commonly used antibiotics of uncomplicated UTIs, has significantly increased in the recent years (4).

UTIs are generally described as infection of the urinary tract and can range from asymptomatic bacteriuria (considered more a contamination than infection), to mild symptomatic UTI, or the most severe manifestation, in form of urosepsis requiring hospitalization (5).

They can be anatomically divided into upper (kidney) and lower (bladder, prostate, urethra) urinary tract infections and further categorized into complicated and uncomplicated. Upper urinary tract infection, as represented by pyelonephritis, is usually caused by pathogens with higher virulence factors and the ability to overcome the host defensive mechanisms. Typical presentations are flank pain, fever and chills. Lower urinary tract infections can be caused by pathogens with weaker, less virulence strength and include cystitis, prostatocystitis and urethritis presenting with dysuria, frequency and urgency.

Uncomplicated UTIs are typically found in female patients without anatomical or structural alterations within the urinary tract, no concomitant diseases known to promote a UTI, as well as the lack of good treatment response (6,7).

On the other hand, complicated urinary tract infections are associated with male sex, conditions which increase the risk of acquiring a UTI or failure of therapy. Risk factors causing complicated UTIs can be elderly population, hospital-acquired infections, pregnancy, indwelling urinary catheters, functional and anatomical abnormalities of the urinary tract, recent antimicrobial use, symptoms presenting for more than 7 days, diabetes mellitus and immunosuppression (6).

Urinary tract infections may cause relapses or reinfections. Relapse of infection refers to reoccurrence of bacteriuria or persistence with the same causative agent as before, whereas reinfection presents with a different microorganism and a new infection. A recurrent UTI is assumed if there are >2 symptomatic episodes of relapses within 6 months or >3 symptomatic episodes within 12 months (7,8).

Asymptomatic bacteriuria, defined as bacteria in the urine without any symptoms is often confused with urinary tract infections by healthcare providers, which leads to unnecessary antibiotic treatment of ABS in older patients (9). It is important to stress out that ABS is a bacterial colonization and does not require antibiotic treatment. Figure 3 provides an algorithm of how to approach the diagnosis of ASB and urinary tract infection. Asymptomatic bacteriuria is commonly found in women affected by recurrent UTIs, especially after being treated with antimicrobial agents. Patients often carry the same bacterial strain for months or years without the evidence of an infection (5,10).

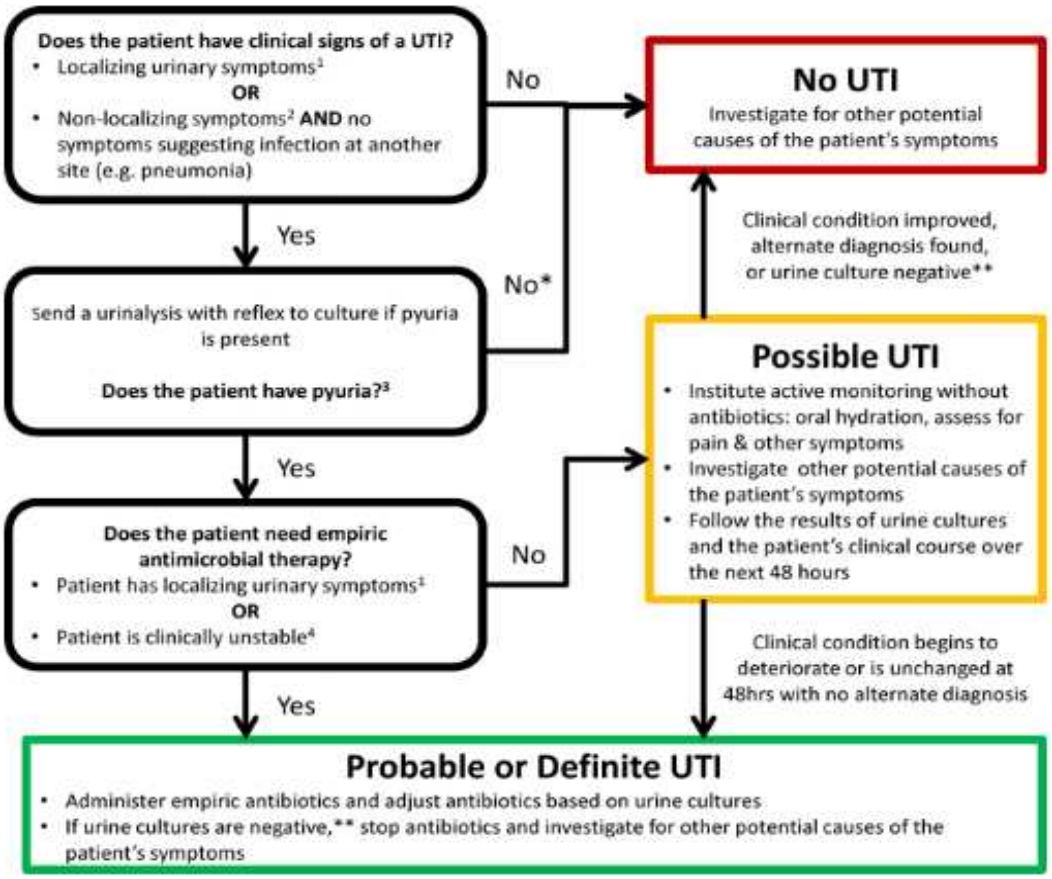

Figure 3. Algorithmic approach to diagnosing ASB and Possible, Probable or Definite UTI

Source taken from: Cortes-Penfield NW, Trautner BW, Jump RLP et al. Urinary Tract Infection and Asymptomatic Bacteriuria in Older Adults. Infect Dis Clin North Am.2017;31(4):673-688 (9).

In otherwise healthy women ABS prevalence increases to about 20% over the age of 70 years and can even range from 25 to 50% in women, 15 to 40% in men in long-term care facilities (11,12). The importance in differentiating ABS and true urinary tract infection is based on the decision making of whether to treat a possible infection or not. Even though UTIs in elderly women, especially if ascending to the upper urinary tract, can have serious consequences; several randomized control trial found that 25% to 50% of women presenting with UTI symptoms will have recovered in 1 week without the use of antibacterial therapy. This shows that if the diagnosis of a UTI is within doubt, using supportive treatment such as increased fluid intake is more helpful than giving antibiotics blindly (10). Studies further suggest that ABS protects the host against symptomatic infections with more virulent strains and by this even reduces the risk of recurrent urinary tract infections, where rapidly increasing antibiotic resistance poses a threat (11).

Duration of catheterization, a commonly medical performed procedure in elderly, represents the greatest risk factor for catheter-associated UTI. Hence guidelines provided by the Infectious Diseases Society of America (IDSA) recommend that catheters that have been in use for more than 2 weeks should be changed to try and lead to quicker resolution of symptoms and prevent UTI recurrence. The optimal method of decreasing catheter associated UTI would be to reduce indwelling catheter use and earliest possible removal of catheters the moment they are no longer clinically indicated (13).

There are discrepancies in causative agents causing nosocomial urinary tract infections and outpatient infections. The predominant uropathogen causing acute uncomplicated cystitis and uncomplicated pyelonephritis especially in outpatient settings for several decades is and has been *E.coli.* Recurrent infections, complicated or nosocomial infections are increasingly caused by *Proteus, Pseudomonas, Klebsiella, Enterobacter species* or multiple organisms simultaneously (8,14).

1.3. Risk factors for developing urinary tract infections

Elderly population is especially susceptible to bacterial urinary tract infections and increasing age poses a risk factor itself. It is a multifactorial risk including higher prevalence of urinary incontinence and urinary retention, urinary catheterizations, long-term medical institutionalization and decreased immunocompetence (9).

Diagnosis of UTI in elderly can be challenging due to a less typical presentation of symptoms as seen in younger patients which can make the diagnosis less accurate. Co-morbidities and age related structural and functional changes of the urinary tract often complicate the clinical assessment. Deafness, neurologic diseases or cognitive deterioration can make the history taking, information about signs and symptoms and communication with the patient problematic (13).

Particular attention should be paid to prior history of colonization or infection with multidrug-resistant organisms (MDROs), as well as prior antibiotic usage in the preceding months, because both represent risk factors for infections with resistant bacteria (9).

Another important risk factor for UTIs and bacterial prostatitis for male patients are prostate enlargement, also called benign prostatic hyperplasia (BPH). It is a structural abnormality that is mostly associated with ageing and most often affects men > 60 years of age and older. Due to the chronic state that prevents the bladder from emptying completely, the likelihood that bacteria will grow and trigger an infection is increased (15).

Other factors such as incontinence, dementia, malnutrition, and impairment of daily activities can additionally predispose the elderly population to UTIs (16,17).

Several neurological conditions such as cerebrovascular disease, Alzheimers disease, and Parkinson´s disease are all diseases of old age and represent a risk factor due to impaired bladder emptying.

For female patients postmenopausal estrogen deficiency has been linked with recurrent UTI. Cystoceles, significant post-voiding residual urine volumes, and incontinence are all associated with recurrent UTI in elderly women. A variety of urological condition that can cause obstruction such as stones or tumor also increases the risk of infection (13).

In old age the distribution between gender is not as extreme as in younger age, with female to male ratio of 2:1 in older patients, compared to 50:1 in younger populations, due to the risk factors of old age, mentioned before (4).

Elderly diabetics have a five-fold higher mortality risk due to urinary tract infections than elderly non diabetics. The body´s ability to fight against pathogens by a weaker immune system, which may lead to a greater frequency and severity of certain infections, especially foot infections, yeast infections, surgical site infections and especially urinary tract infections are increased in diabetics. Poor circulation, reduced ability of the white blood cells to fight infections, poorly contracting and dysfunctional bladders are responsible to higher prevalence of UTIs in the diabetic population (18).

1.4. Pathophysiology of UTI

Urinary tract infections occur when the bacterial virulence factors manage to overcome the highly efficient host defensive mechanisms. There are three routes by which bacteria can invade the urinary tract: by ascending, being the most common, hematogenous and lymphatic pathways.

The normal urinary tract is resistant to colonization by bacteria, except for urethral mucosa. Several lower urinary tract antibacterial defensive mechanisms exist, as depicted in the table, that efficiently and rapidly eliminate microorganisms that have gained access to the bladder.

The urinary tract is lined by specialized urothelial cells originating from bladder-, or ureteral-urothelial cells. Important biological functions are performed by this specialized epithelium as the formation of physically stable apical surface, highly effective permeability barrier and formation of uroplakin-containing urothelial plaques. Uroplakins play an important role in the pathogenesis of urinary tract infections, expressing unmodified mannose residues that can interact with type q-fimbriated uropathogenic *E.coli* (UPEC) and help bacteria to resist the flow of urine. Other urothelial cell layers differ in characteristics as morphology, and potential to support intracellular bacterial growth. For example, umbrella-cell layers of the bladder-urothelial cells are the place where UPEC strains are most commonly found, causing acute cystitis. Intermediate and basal cell layers are more associated with providing quiescent intracellular reservoirs, typical for recurrent UTIs (1).

The presence of healthy urinary microbiome is important in preventing UTIs by multiple mechanisms, such as occupying attachment sites at the genitourinary epithelium, competing for nutrients and limiting proliferation potential of uropathogens via bacteriophage infection. When there is persistent urinary dysbiosis, comparably seen with the disruption of intestinal microbiota due to antibiotic overuse leading to Clostridium difficile infection, the host defences of the urinary tract can be impaired and be predisposed to recurrent UTIs (9).

Due to its high prevalence, *E.coli* virulence is the best studied so far. *E.coli* have multiple subtypes with different strains exhibiting differences in O, K, and H antigens. The serotypes are associated with presence and expression of multiple chromosomal virulence factor determinants, that enable the bacteria to adhere to vaginal and uroepithelial cells and develop resistance to serum bactericidal activity. By expressing higher quantity of K antigen in capsules, bacteria are more protected from leukocyte phagocytosis.

Other virulence factors include aerobactin, cytotoxic necrotizing factor type 1, hemolysin, which facilitate tissue invasion and cause renal tubular epithelial and parenchymal

cell damage. Adhesins (p-fimbriae, other mannose-resistant adhesins, type 1 fimbriae) allow attachment and adherence to uroepithelial cell membrane (6,8,15).

More specific, P fimbriae enable the binding of *E.coli* to cell receptors containing globoseries glycosphingolipid and are mannose-resistant since they are not inhibited by mannose, as is the binding of type I fimbriae to mannose-containing host epithelial receptors, glycoproteins uroplakin I and II. It enables P fimbriae to remain longer in the intestinal tract and spread more efficiently to the urinary tract causing colonization and producing ascending infection where they tend to adhere, persist and invade the kidney and may induce bacteremia. Type I fimbriae is expressed in almost all strains causing cystitis, but not commonly found among pyelonephritic strains.

Motility of bacteria that aid with ascending against the flow of urine, production of endotoxins by gram-negative bacilli that can decrease ureteral peristalsis and possibly contribute to renal parenchymal inflammatory response by phagocytic cell activation represent further virulence factors. *Proteus ssp*. show the unique production of ureases that can changes the pH, creating a favourable environment for the bacteria and enable the pathogen to cause pyelonephritis (6,14).

The production of this extracellular polysaccharide polymers or “slime factor” acts as a structure with defined architecture, providing the microorganisms with excellent protective environment (less susceptible to antibiotics) and favouring the exchange of genetic material (virulence and antibiotic resistance determinats) between cells as well as intercellular communication (15).

1.5. Resistance and epidemiology

The ability of bacteria to develop antimicrobial resistance is a natural phenomenon and represents a major health care problem in the treatment of infections. Development of resistances is a complex process which can start by mutation in bacterial genes or acquisition of exogenous resistance genes carried by mobile genetic elements, which can be passed along between bacteria. Bacteria can acquire multiple mechanisms of resistance to several antimicrobial drugs, greatly limiting the available treatment options. As before mentioned the origin of occurrence and spread of resistance can be lead back to overuse of antimicrobial agents exerting ecological pressure on bacteria and the transmission of acquired resistance mechanisms between bacteria especially in health care facilities (19).

Currently, multidrug-resistant (MDR) gram-negative bacteria pose a threat in hospitals as well as nursing homes. The recent Annual Report of the European Antimicrobial Resistance Surveillance Network (EARS-Net) showed large MDR variations across Europe, being higher in southern and south-eastern Europe than in northern Europe.

Multidrug resistance can be defined as non-susceptibility to at least one agent in three or more antimicrobial catergories (extended-spectrum penicillins, carbapenems, cephalosporins, aminoglycosides, and fluoroquinolones) (20).

E.coli is by far the most frequent cause of urinary tract and bloodstream infections in both community and health care origin. Mutations, as seen to fluoroquinolones, or acquisition of mobile genetic elements encoding resistance mechanisms, for example extended spectrum beta-lactamases (ESBLs) and carbapenemases are reasons for antibiotic resistance. ESBLs are enzymes able to confer resistance to most beta-lactam antibiotics, such as third generation cephalosporins. Carbapenems might remain one of the few therapy options for server infections, usually being able to resist the ESBL action. Recently emerging carbapenem resistance is reason to worry for any antibacterial agent staying effective against the resistances.

According to EARS-Net the highest EU/EEA population-weighted mean resistance percentage for *E.coli* was reported for aminopenicillins (58.7%), followed by fluoroquinolones (25.7%), third-generation cephalosporins (14.9%) and aminoglycosides (11.4%) in 2017 and is depicted in Figure 4. Carbapenem resistance fortunately remained rare, but significant increasing trends in population-weighted mean percentages of fluoroquinolone and third-generation cephalosporin resistance have been recorded at the EU/EEA level between 2014 and 2017.

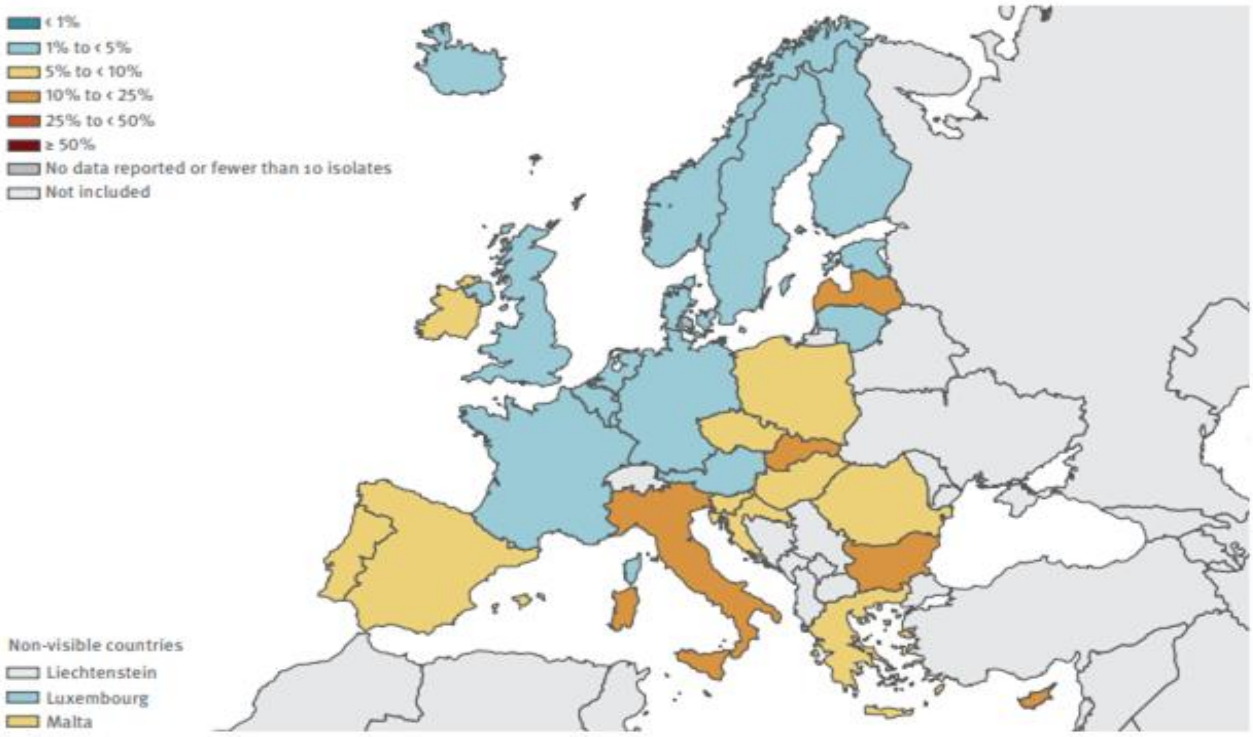

Figure 4. *Escherichia coli*. Percentage (%) of invasive isolates with combined resistance to third-generation cephalosporins, fluoroquinolones and aminoglycosides, by country, EU/EEA countries, 2017 (21).

Source taken from: ecdc.europa.eu [Internet]

Klebsiella pneumoniae can be resistant to multiple antimicrobial agents, and resistance traits can be acquired through plasmids. In contrast to *E.coli, K. pneumoniae* has a chromosomally encoded class, a beta-lactamase and is in this way intrinsically resistant to aminopenicillins. Increasing resistance of *Klebsiella* to fluoroquinolones has been reported as well, limiting the treatment options.

Pseudomona aeruginosa is intrinsically resistant to the majority of antimicrobial agents due to its ability to prevent various antibiotic molecules from penetrating its outer membrane or to extrude them. The few antimicrobial groups that remain active include fluoroquinolones, aminoglycosides, and some beta-lactams, although resistance of *P. aeruginosa* to these agents can be acquired through several mechanisms, including modified antimicrobial targets, efflux, reduced permeability and degrading enzymes. In 2017 the highest EU/EEA population-weighted mean resistance percentage again was reported for fluoroquinolones (20.3%), followed by piperacillin ± tazobactam (18.3%) (20,21).

1.6. Diagnosis

In as many as 40% of hospitalized older patients UTIs are incorrectly diagnosed, as studies have been suggesting. This high number and increasing prevalence of health care associated infections and emerging antibiotic resistance highlights the importance of obtaining a firm diagnosis, the treatment with appropriate antibiotic agents and avoidance of broad-spectrum antibiotics (13).

The sole usage of urinary dipstick testing, urinanalysis, and urinary culture is challenging in older adults due to the high prevalence of bacteriuria and pyuria that may not be clinically significant (5).

Urinary dipstick testing is an easy and convenient analysis that should primarily be used to rule out and not establish a diagnosis of UTI due to its high test characteristic variability. Especially in older adults, sensitivity and specificity of leukocyte esterase and nitrates detection with urinary dipstick testing, varies greatly. It ranges from a positive predictive dipstick test with 82% (95% CI, 74%-92%) and 71% (95% CI, 55%-71%) respectively, to negative predictive value from 92% to 100% in other studies (5).

Furthermore the sole usage of urine culture does not establish the diagnosis of UTI but aids in the selection of appropriate treatment (13).

It can be challenging for clinicians caring for older patients with chronic nonspecific symptoms to know when to order urine laboratory studies. Fever, acute dysuria (<1week in duration), new or worsening urinary urgency, frequency, new urinary incontinence, gross hematuria, suprapubic or costovertebral angle pain or tenderness, are indications to obtain urine studies. Non-specific signs as persistent changes in mental status, change in character of the urine not responding to other interventions can suggest the need of urine studies in patients with cognitive impairment (5). Studies suggest that urine should not be sent for culture on the basis of positive urine dipsticks if no symptoms are evident (13).

Asymptomatic bacteriuria is defined as presence of at least 10^5 colony forming unit (cfu) or uropathogenic bacteria per milliliter in two consecutive voided urine specimens of a clean-catch midstream urine sample obtained from an asymptomatic patient (5,10).

It is important to clearly define and understand the terms bacteriuria and pyuria and not automatically interpret it as a disease. Bacteriuria is defined as the presence of bacteria in urine on microscopy or quantitative culture, on the other hand pyuria represents white blood cells in urine. Pyuria is sensitive but not specific for UTI and can be associated with other conditions than infection, for example urinary catheters, tumors and stones. Reliance on

pyuria alone for the diagnosis of UTI would lead to overtreatment with antibiotic agents (9,13).

Patients with UTI demonstrate a combination of both pyuria and bacteriuria. Moreover pyuria presents with positive leukocyte esterase on urine dipstick or >10 white blood cells per high powered field (WBCs/hpf) on urine microscopy. These thresholds offer a high negative predictive value for urine culture positivity and clinical UTI. On the other hand bacteriuria is defined as at least 10^5 colony forming units (cfu) per ml of single organism in the urine of a patient who is catheterized or who has had a urinary catheter in the preceding 48 hours (5,9).

Urinary catheters serve as portal of entrance and source of continuous bacterial immigration into the bladder, making bacteriuria ubiquitous in catheterized patients. Attention should be paid to patients with indwelling catheters developing fever, rigors, delirium or costovertebral tenderness, possibly representing a catheter-associated UTI (CAUTI) (9).

Table 1. Cut-off values (colony forming units/ mL) for the diagnosis of different urinary tract infections and asymptomatic bacteriuria (7).

Diagnosis	Evidence of bacteria, CFU/mL	Urine collection
Acute uncomplicated cystitis in women	10^3	Midstream urine
Acute uncomplicated pyelonephritis	10^4	Midstream urine
Asymptomatic bacteria	10^5	In women: evidence in 2 consecutively midstream urine samples. In men: evidence in 1 midstream urine sample. For catheter urine: 10^2 CFU/mL

Hence the gold standard in establishing diagnosis of UTI in older patients requires a combination of signs and symptoms of UTI (>2 genitourinary signs and symptoms) and

laboratory confirmation of urine examination, including quantitative urine culture and its assessment of UTI (bacteriuria and pyuria) (5,7).

1.7. Treatment

Urinary tract infections are among the most common indications for antibiotic prescription in community and health care service and at the same time a big concern due to antibiotic resistance among uropathogens that has significantly increased during the last years (15,22).

With uncomplicated cystitis the clinical presentation is mostly suggestive of *E.coli*, the most common cause of uncomplicated UTI, with predictable susceptibility where narrow spectrum agents are appropriate for empiric treatment initiation. In complicated UTIs on the contrary antimicrobial susceptibility is not as predictable or might be caused by multiple uropathogens and make broad spectrum agents a more appropriate choice.

The importance of antimicrobial stewardship and consideration of collateral damage such as adverse effects, drug toxicity, necessary dose adjustments on GFR of individual patients as well as occurrence of drug resistance has to be integrated in the decision making process as emphasized by IDSA guidelines (23).

Choice of the right antimicrobial agent depends on pharmacokinetic properties and side of infection. Complicated UTIs for example require agents that can achieve high concentrations in urine, kidney tissue and prostate. Nitrofurantoin and fosfomycin, considered first line therapy for uncomplicated UTIs, lack those properties and are therefore not recommended for upper urinary tract infections. In this case fluoroquinolones which have broad spectrum activity and readily penetrate tissue would be the drug of choice, but have limited use due to high resistance rates in certain areas. Trimethoprime and sulfamethoxazole (TMP-SMX), also recommended as first line agents by the IDSA, penetrate tissue effectively and are an excellent alternative if the organism is known to be susceptible (9,24).

De-escalation of broad-spectrum antimicrobial agents to narrow spectrum agents, as soon as susceptibility results are available, is an important strategy in antimicrobial stewardship.

Decision making about route of administration and selection of the correct dose are as well necessary considerations for the right therapy approach. There are antimicrobials that are characterized by concentration-dependent killing (e.g. aminoglycosides and fluoroquinolones) and are thus most effective when administered once daily, achieving high

serum or tissue peak concentration. On the contrary antimicrobials acting by time-dependent killing (e.g. penicillins and cephalosporins), are more effective when serum or tissue concentrations are maintained above the minimum inhibitory concentration (MIC) for a prolonged time period. This is typically accomplished by prolonged or continuous infusions of the drug. With complicated UTIs oral agents should be able to achieve high serum concentrations, whereas parenteral route is typically preferred for empiric treatment in severely ill patients or those with poor absorption or bioavailability (24).

Another important step of therapy planning is to determine the duration of treatment, if short course antimicrobial therapy is sufficient or a longer duration is needed. Antimicrobial management of acute uncomplicated cystitis or UTIs is typically treated with short course regimens, varying from 1 to 5 days (9,24).

Empirical first line agents for uncomplicated cystitis according to the IDSA guidelines include: nitrofurantoin administered over five days of therapy, trimethoprim-sulfamethoxazole given over a three day course, fosfomycin as single dose, and pivmecillam. Table 2 describes dosages and daily application in more detail. (9,23,24).

The treatment with fluoroquinolones, considered second line agents in uncomplicated UTIs, is a popular choice due to its high bioavailability and broad-spectrum coverage. Nevertheless its usage is controversial since the prevalence of resistance is rising and should be reserved for other infections then uncomplicated UTIs. The FDA states the risks of this group of antibiotics would outweigh their benefits when other agents are available for treatment. Beta-lactams (e.g. amoxicillin-clavulanate) over a 7-day course may for example be considered as an alternative for second line treatment.

Summarizing the official recommendations, nitrofurantoin, TMP-SMX, fosfomycin and pivamecillinam are considered first line agents, but are not applicable for empiric treatment if they exceed the thresholds for the prevalence of resistance of 10% for fluoroquinolones and 20% for TMP-SMX respectively. Despite the increasing prevalence of resistance to TMP-SMX, IDSA recommends its use as first-line agent in uncomplicated UTI if patients have not received antibiotics or been hospitalized in the past 3 months, and there is <20% resistance regionally. Fosfomycin is one of the few remaining oral agents with reliable activity against ESBL-producing uropathogens, and should hence be reserved for pathogens known to express ESBL (13,24).

Table 2. Antimicrobial management of acute uncomplicated cystitis [a].

Antimicrobial	Dosing and Duration	Efficacy
First-Line Agents		
Nitrofurantoin monohydrate/macrocrystal [b]	100 mg twice daily × 5 days (with meals)	• Clinical efficacy of 5–7 day regimen: 93% (84%–95%) • 3–day regimen appears less effective *vs*. longer regimens • Minimal *in vitro* resistance
Trimethoprim-sulfamethoxazole [c]	160/800 mg twice-daily × 3 days	• Clinical efficacy of 3-day TMP-SMX regimen: 93% (90%–100%) • Avoid if resistance >20% or exposure in prior 3–6 months
Fosfomycin trometamol	3 g sachet in a single dose	• Appears to be less effective *vs*. TMP-SMX or fluoroquinolones • Minimal *in vitro* resistance, but most labs do not test
Pivmecillinam	400 mg twice daily × 3–7 days	• Clinical efficacy of 3–7 day regimens: 73% (55%–82%) • Minimal *in vitro* resistance • Unavailable in some countries
Second-Line Agents		
Fluoroquinolone: Ciprofloxacin [c] Levofloxacin [c]	250 mg twice daily × 3 days 250 mg or 500 mg once daily × 3 days	• Clinical efficacy 90% (85%–98%) • High prevalence of *in vitro* resistance in some regions of the world
β-lactam [b]:(e.g., amoxicillin-clavulanate, cefdinir, cefaclor, and cefpodoxime-proxetil)	3–7 days	• Clinical efficacy of 3–5 day regimens: 89% (79%–98%) • Less effective thanTMP-SMX and fluoroquinolones • Prevalence of *E. coli* resistance is variable

Adapted from ref. [2]. [a] Efficacy data and antimicrobial recommendations based on IDSA guidelines [13]; [b] Pregnancy category B—no clear risk to fetus based on animal and/or human studies; [c] Pregnancy category C—animal studies have shown an adverse effect on the fetus; use only if potential benefit justifies the potential risk to the fetus.

Source taken from: Abbo LM, Hooton TM. Antimicrobial Stewardship and Urinary Tract Infections. Antibiotics. 2014;3(2):174-192 (24).

Pyelonephritis is a serious infection and broad-spectrum empiric treatment should be started without delay, followed by adaptation to urine cultures and susceptibility of bacteria. Severe manifestations of the infections, hemodynamic instability, oral medication intolerance, poor compliance or any other complicating factor should include hospitalization of the patient. Long term duration therapy of at least 7 days, especially in men with underlying prostatic infections, is indicated to prevent complications such as perinephritic abscess or bacteremia.

Empiric treatment for pyelonephritis includes short-course therapy with fluoroquinolones, long duration therapy with TMP-SMX for 7-14 days or alternatively beta-lactams for 10-14 days. Parenteral administration of ceftriaxon can be added if drug resistance is suspected (9,24, Table 3).

Table 3. Antimicrobial outpatient management of acute uncomplicated pyelonephritis [a].

Antimicrobial	Dosing and Duration	Efficacy
Fluoroquinolone: Ciprofloxacin [b] Levofloxacin [b]	500 mg orally twice-daily or 1 g extended release orally once-daily × 7 days 750 mg orally once-daily × 5 days	• Clinical efficacy of ciprofloxacin 500 mg orally twice daily for 7 days: 96% Clinical efficacy of levofloxacin 750 mg orally or intravenous once daily for 5 days: 86%; *vs.* ciprofloxacin 400 mg intravenous or 500 mg orally twice daily for 10 days: 81%; most subjects in both arms received oral therapy
Trimethoprim-sulfamethoxazole [b]	160/800 mg orally twice-daily for 14 days	• Inferior choice for empirical therapy due to high rates of resistance and corresponding failure rates • Highly effective if strain susceptible • *E. coli* resistance >20% in many areas of world, including some areas of the US • 92% clinical efficacy if *E. coli* susceptible *vs.* 35% if not susceptible)
Oral β-lactam Specific agents are not listed in IDSA guidelines	Duration 10–14 days	• Data limited, but inferior efficacy *vs.* TMP-SMX and fluoroquinolones • Oral β-lactams should be used only when other recommended agents can't be used

Adapted from ref. [2]. [a] Efficacy data and antimicrobial recommendations based on IDSA guidelines [13]; [b] Pregnancy category C—animal studies have shown an adverse effect on the fetus; use only if potential benefit justifies the potential risk to the fetus.

Source taken from: Abbo LM, Hooton TM. Antimicrobial Stewardship and Urinary Tract Infections. Antibiotics. 2014;3(2):174-192 (24).

Asymptomatic bacteriuria is a very common problem among elderly and a highly discussed topic whether to treat or not in the health care system. It is important to understand that mismanagement of asymptomatic patients with positive urine cultures could promote antimicrobial resistance and results in unnecessary antimicrobial-related adverse events and increased health care costs. Over-interpretation of urinalysis that weighs too much emphasis on presence of pyuria, nitrite positivity, and higher bacterial counts are the cause of it. Despite multiple recommendations and guidelines suggesting not to treat this condition, ASB remains one of the most common causes of antimicrobial over-prescription in both acute and long term care (25,5).

The 2019 guidelines from the Infectious Disease Society of America clearly recommend that ASB should be screened and treated only in pregnant women or in an individual undergoing invasive urological procedures, and not recommended in healthy women, older women or men with diabetes, indwelling catheter, or spinal cord injury. Despite the fact that antimicrobial drug therapy is effective in eradicating bacteriuria in ASB, it has been shown that reinfection rates, adverse antimicrobial drug effects, and increasing resistant organisms occur more commonly in patient groups being treated for ASB (24-26).

There is the shift towards alternative non-antibiotic approaches, such as probiotic supplementation, cranberry substrates trying to reduce antibiotic therapy in managing recurrent UTIs, although not proven to show consistent benefit yet.

A critical step in recurrent urinary tract infections includes the adhesion of bacteria to uroepithelium, as previously described in the pathogenesis of UTIs, which could be approached as potential drug target. This is the hypothesis for using cranberry procanthocyanidins in many studies, which is suggested to inhibit adherence of *E.coli* P-fimbriae to uroepitelial cells, although studies have failed to prove a clinically relevant effect in UTI prevention so far (9).

On the other hand prophylaxis with low-dose antibiotics and vaginal estrogens in postmenopausal women has shown to reduce the rate of UTIs. Norwegian guidelines thus recommend low dose of TMP and nitrofurantoin effective as UTI prophylaxis in nursing home residents being affected with high prevalence. Vaginal administration of estrogens and cranberries are also here suggested but have shown a lower grade of evidence (27).

2. OBJECTIVES

Aim:

The aim of this study was to investigate the most common etiology of bacteria causing urinary tract infections and their antibiotic sensitivity in patients aged over 65 years old, being treated in the University Hospital of Split, in 2018.

Hypotheses:

1. Elderly patients coming to the Infectology department of University Hospital of Split are more frequently infected with resistant bacterial strains.

2. Empirical treatment should include broad-spectrum antibiotic therapy before results of urinary culture with antibiograms, revieling antibiotic sensitivity, can be taken into consideration for the appropriate therapy continuation.

3. MATERIALS AND METHODS

3.1. Study population

This study included 107 patients over 65 years of age with the diagnosis cystitis, acute prostatocystitis, acute pyelonephritis and urosepsis, which were treated at the Clinic of Infectology at the University Hospital of Split, in 2018. 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 were 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, stored in the archive. The collected data was inserted into Microsoft Excel program.

3.4. Research Method

By evaluating the medical files of the patients included in this study, different diagnosis of urinary tract infections were collected and the occurrence in age groups were analysed. Laboratory results of microbiology antibiogram testing of isolated organisms extracted from urine cultures made the presentation of the etiology of infection and the sensitivity to antibiotic agents of the pathogens possible.

4. RESULTS

Our study included 107 patients in total aged 65 years or above. Table 4. depicts the gender distribution by differnet age groups. The highest number of patients was found in the oldest category >85 years and older. Men and women were almost equally often treated for UTI in 2018, with only slightly higher prevalence in women with 54,2% then men (45,8%).

Table 4. Distribution of patients with urinary tract infections (UTIs) according to age and sex

Age (years)	**Female N, (%)**	**Male N, (%)**	**Total N, (%)**
65-69	5	11	16 (15.0)
70-74	16	11	27 (25.2)
75-79	5	7	12 (11.2)
80-84	14	10	24 (22.4)
>85	18	10	28 (26.2)
Total	58 (54.2)	49 (45.8)	107 (100.0)

In Table 5. the distribution of clinical diagnosis is presented. The highest number of clinical diagnosis for patients aged >65, being treated for urinary tract infections in the Clinic of Infectology in 2018, was urosepsis with 37,4%, closely followed by pyelonephritis acuta with 36,4%, with only one patient number difference. The least common encountered diagnosis was cystitis acuta, in only 4 patients with 3,7%.

Table 5. Clinical diagnosis of patients with UTI

Diagnosis	**Number (%)**
Urosepsis	40 (37.4)
Pyelonephritis acuta	39 (36.4)
Cystopyelitis acuta	15 (14.0)
Prostatocystitis	9 (8.4)
Cystitis acuta	4 (3.7)
Total	107 (100.0)

Table 6. gives an overview of the etiology of urinary tract infections acquired from urine culture. Of all bacterial isolates (N=107), the most frequent isolated organism was *Esherichia coli* with 43,9%, followed by *Proteus mirabilis* with 15%, *and Pseudomonas aeruginosa* with 9%.

Table 6. Etiology of UTI

Agent	**Urine Culture (N)**	**Urine culture N, (%)**
E.coli	54	50.5
Proteus mirabilis	16	15.0
Pseudomonas aeruginosa	12	11.2
Klebsiella pneumoniae	10	9.4
Enterococcus faecalis	4	3.7
Enterobacter sp.	2	1.9
Citrobacter freundii	1	0.9
Enterobacter cloacae	1	0.9
Enterococcus sp.	1	0.9
Morganella morganii	1	0.9
Providencia stuartii	1	0.9
Providentia sp.	1	0.9
Providentia sp. ESBL	1	0.9
Staphylococcus aureus MSSA	1	0.9
Total	107	100.0

Table 7. shows the sensitivity and resistance rates of *E.coli* to different antibiotic agents. The resistance was highest towards ampicillin with 51,9%, followed by fluoroquinolones with 27,8%, then amoxicillin-clavulanic acid and 1st generation cephalosporin (cefalexin), where the resistance rates were 24,1% for both. Not one isolate of *E.coli* was found to be resistant to carbapenems.

Table 7. Antibiotic sensitivity of *Esherichia coli* in patients aged >65 with urinary tract infections

Antibiotic	**Sensitive N, (%)**	**Resistant N, (%)**	**Total Number**
Ampicillin	25 (48,1)	27 (51,9)	52
Amoxicillin-clavulanic acid	41(75,9)	13 (24,1)	54
Cephalosporin 1st generation (cefalexin)	41 (75,9)	13 (24,1)	54
Cephalosporin 2nd generation (cefuroxime)	42 (77,8)	12 (22,2)	54
Cephalosporin 3rd generation (ceftriaxone)	43 (79,6)	11 (20,4)	54
Cephalosporin 4th generation (cefepime)	45 (83,3)	9 (16,7)	54
Fluoroquinolones (ciprofloxacin)	39 (72,2)	15 (27,8)	54
Nitrofurantoin	48 (94,1)	3 (5.9)	51
Aminoglycosides (gentamicin)	46 (86,8)	7 (13,2)	53
Carbapenems (imipenem)	54 (100)	0 (0)	54

The second most common isolated pathogen in our study was *Proteus mirabilis*, showing high resistance rates to nitrofurantoin with 100%, followed by fluoroquinolones with 68,7%, and by ampicillin, amoxicillin-clavulanic acid and the first three cephalosporin generations, all showing resistance rates of 56,2%. According to our findings, *P.mirabilis* exhibited 100% sensitivity to both piperacillin-tazobactam and carbapenems , followed by 4th generation cephalosporins with 87,5%.

Table 8. Antibiotic sensitivity of *Proteus mirabilis* in patients aged >65 with urinary tract infections

Antibiotic	**Sensitive N, (%)**	**Resistant N, (%)**	**Total Number**
Ampicillin	7 (43,7)	9 (56,2)	16
Amoxicillin-clavulanic acid	7 (43,7)	9 (56,2)	16
Piperacillin - Tazobactam	16 (100)	0 (0)	16
Cephalosporin 1st	7 (43,7)	9 (56,2)	16
Cephalosporin 2nd	7 (43,7)	9 (56,2)	16
Cephalosporin 3rd	7 (43,7)	9 (56,2)	16
Cephalosporin 4th	14 (87,5)	2 (12,5)	16
Fluoroquinolone	5 (31,2)	11 (68,7)	16
Aminoglycosides	7 (43,7)	9 (56,2)	16
Nitrofurantoin	0 (0)	16 (100)	16
Carbapenems	16 (100)	0 (0)	16

Table 9. presents *Pseudomona aeruginosa* isolates, showing 100% sensitivity to piperacillin-tazobactam and 3rd generation cephalosporins. Only 10 of the 12 isolated organisms were tested for antibiotic sensitivity to carbapenems, revealing 80% sensitivity, whereas sensitivity to fluoroquinolones was only 41,7% and to aminoglycosides 58,3%.

Table 9. Antibiotic sensitivity of *Pseudomons aeruginosa* in patients aged >65 with urinary tract infections

Antibiotic	**Sensitive N, (%)**	**Resistant N, (%)**	**Total Number**
Piperacillin - tazobactam	12 (100)	0 (0)	12
Cephalosporin 3rd (ceftazidim)	12 (100)	0 (0)	12
Cephalosporin 4th (cefepime)	11 (91,7)	1 (8,3)	12
Fluoroquinolone (ciprofloxacin)	5 (41,7)	7 (58,3)	12
Aminoglycosides (gentamicin)	7 (58,3)	5 (41,7)	12
Carbapenems (imipenem)	8 (80,0)	2 (20,0)	10

Klebsiella.pneumoniae organisms isolated in our study have shown high resistance rates to almost all investigated antibiotic agents compared to the other bacteria isolated and are represented in Table 10. The highest resistance is present towards ampicillin with every single organism isolated resistant to it, followed by fluoroquinolones with 80% resistance, all cephalosporin generations with 60% and 50% to aminoglycosides. The highest sensitivity was exhibited for carbapenems with 80% and to piperacillin-tazobactam with 70%.

Table 10. Antibiotic sensitivity of *Klebsiella pneumoniae* in patients aged >65 with urinary tract infections

Antibiotic	Sensitive (%)	Resistant (%)	Total Number
Ampicillin	0	10 (100)	10
Amoxicillin-clavulanic acid	5 (50)	5 (50)	10
Piperacillin-tazobactam	7 (70)	3 (30)	10
Cephalosporin 1st	4 (40)	6 (60)	10
Cephalosporin 2nd	4 (40)	6 (60)	10
Cephalosporin 3rd	4 (40)	6 (60)	10
Cephalosporin 4th	4 (40)	6 (60)	10
Fluoroquinolone	2 (20)	8 (80)	10
Aminoglycosides	5 (50)	5 (50)	10
Carbapenems (imipenem)	8 (80)	2 (20)	10

Table 11. displays sensitivity and resistance rates for 5 *Enterococcus* organisms isolated in our study. High sensitivity rates with 100% for nitrofurantoin, vancomycin and linezolid, and 80% to ampicillin, amoxicillin-clavulanic acid and carbapenems were proven.

Table 11. Antibiotic sensitivity of *Enterococcus ssp*. in patients aged >65 with urinary tract infections

Antibiotic	Sensitive (%)	Resistant (%)	Total Number
Ampicillin	4 (80,0)	1 (20,0)	5
Amoxicillin-clavulanic acid	4 (80,0)	1 (20,0)	5
Fluoroquinolone (ciprofloxacin)	3 (60,0)	2 (40,0)	5
Nitrofurantoin	5 (100)	0 (0)	5
Carbapeneme (imipenem)	4 (80,0)	1 (20,0)	5
Vancomycin	5 (100)	0 (0)	5
Linezolid	5 (100)	0 (0)	5

5. DISCUSSION

High resistant rates of uropathogens encountered in elderly patients treated in our Infectology Clinic in Split, drive us to use broad-spectrum antibiotic agents when treating UTIs empirically.

Urinary tract infections are the most frequent encountered infections of elderly in primary care offices as well as hospital settings and can impose a significant cause of morbidity among older patients (5,9).

The increased prevalence of UTIs encountered in elderly population is connected with an increase of risk factors, which are attributed to aging. Anatomical and structural abnormalities of the genitourinary tract, incontinence, comorbidities, neurologic conditions with loss of autonomy, benign prostatic hyperplasia in male patients are only few of the factors predisposing elderly to require urinary tract infections. Our study focused on patients being 65 years of age or older and in accordance to the previously mentioned, the highest number of patients hospitalised for urinary tract infection is found in our oldest age range with 85 years and above, representing 26% of our study sample.

The incidence of UTIs increases with age in both, men and women, being twice more common in women according to literature (4,5). The distribution between the two genders in our study showed slightly more female patients, with 58 female subjects and 49 male patients. This could partially be due to the small sample size or due to the fact that with increasing age other risk factors than sex are predominating. A study has been suggesting that cognitive impairment and disabilities in daily living play a greater role in acquiring urinary tract infections as compared to gender in elderly. Whereas the impact of sex in younger patients with UTIs is much stronger, with a female to male ratio as high as 50:1 as a study suggests (4,16).

Elderly are more prone and vulnerable to infections due to a weakened immune system and often have a more severe course and manifestations of UTIs. The highest encountered diagnosis of UTI found in our study was urosepsis with 37,4%, followed by pyelonephritis with 36,4%. This could be explained by the fact that uncomplicated UTIs, as for example uncomplicated cystitis, are frequently managed in outpatient settings or are often not even recognized. The diagnosis of a UTI can be challenging in older patient population. There has been controversy between different studies. Some suggest over-diagnosis being a frequent problem, by only taking laboratory results like bacteriuria or pyuria into consideration or misdiagnosing asymptomatic bacteriuria as an UTI. Other studies on the other side suggest that atypical symptomatic and clinical presentation of elderly, especially with cognitive impairment or incontinence, make the diagnosis of urinary tract infection

complicated and only obvious with severe manifestations and deterioration of the patient state, as can be seen in urosepsis or upper urinary tract infections (9,13,24,25).

The etiology of UTIs in our study is in accordance to findings of other studies, with *E.coli* causing the infection in 54 subjects and being the most common isolated organism. Far behind *E.coli*, other common pathogens causing urinary tract infections were *Proteus mirabilis, Pseudomona aeruginosa* and *Klebsiella pneumonia* in our, as well as other previous studies (4,5,9,21).

Special emphasis of our study was to investigate antibacterial sensitivity to antimicrobial agents and adapt treatment recommendations according to international guidelines. Guidelines and recommendations need to be constantly updated and renewed and are specific to geographical distribution of bacterial resistance occurrence. They can be of guidance in choosing different first, second and third line therapies, but cannot be generalized and applied to whole Europe. Each country or geographical region must be informed about local resistance patterns and adjust therapy accordingly.

Multi-drug resistant bacteria have become a major healthcare problem not only in Europe, but worldwide. The European Antimicrobial Resistance Surveillance Network (EARS-Net) releases an annual report with updated data to single resistances and MDR rates across Europe. Large variations can be found between northern and south-eastern Europe, with resistance rates being much higher in the latter.

E.coli, especially important as being the most frequent encountered organism in terms of UTIs, showed the highest resistance rate to ampicillin with 51,9%, followed by fluoroquinolones with resistance rate of 27,8% in our study. Our results are corresponding to EARS-Net most recent annual report released in 2017, which summarized *E.coli* resistance to ampicillin across Croatia with 58%, and to fluoroquinolones with 28,2%.

Considering the high resistance rates to fluoroquinolones of isolated *E.coli* organisms in our study we should preclude the usage of fluoroquinolones as 1st line agent in acute uncomplicated pyelonephritis. IDSA clearly advises against its usage when local resistance exceeds 10%. The alternative first-line agent TMP-SMX also shows a high resistance pattern according to EARS-Net data for Croatia and since recommendations only include these agents if resistance is below 20%, this agent also should not be included as first line therapy. Oral ß-lactam sensitivity showed higher susceptibilities in our isolated *E.coli* specimens compared to the previously mentioned antibiotics and hence amoxicillin-clavulanic acid, 4rd generation cephalosporins would be a better choice for initiation of empiric therapy. The highest sensitivity was towards carbapenems with 100% and with certainty ensures treatment

success. It should be considered as initial treatment for patients with severe infection and high probability for UTI related complications. Increasing carbapenem resistance poses a threat in our community, since it is often considered last resort treatment and should be saved for severe cases. EARS-Net surveillance report states that resistance to carbapenems in *E.coli* remains rare in Europe, which we can confirm with our results, with not a single isolated *E.coli* organism exhibiting resistance to it.

Nitrofurantoin considered first-line agent for acute uncomplicated cystitis by the IDSA as well as by official guidelines provided by the German medical expert association - Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften e.V. (AWMF), exhibited high sensitivity in our study with 94,2% making this agent a reliable first choice for therapy.

Similarly high resistance behaviour to first line agents for the treatment of pyelonephritis, as discussed with *E.coli*, is true for *Proteus mirabilis*. Since the resistance rate to fluoroquinolones and TMP-SMX again exceed their resistance thresholds to include them as first line option, piperacillin-tazobactam, displaying 100% sensitivity, or 4th generation cephalosporins would be a more appropriate choice for treatment initiation.

Worrisome are data reported by EARS-Net for *K. pneumoniae*, with above 10% acquired resistance rates to carbapenems across Europe. Our study showed even double as high resistance patterns, with 20%. The discrepancy between EARS-Net data and our findings could be a result of EARS-Net summarizing resistance percentages for all European countries together in one percentage rate, including the low resistance rates from northern countries and by this displaying overall lower resistance rates. This again emphasizes the need of being aware of updated data in the own local geographical region, varying greatly from country to country (21,28).

Besides trying to avoid unnecessary use of antibiotics to avoid resistance emergence, therapy of infections especially in older patient population must be taken serious and carefully evaluated. Elderly are more susceptible and often suffer from serious consequences of urinary tract infections as dehydration, delirium, urosepsis or even death (16). Incidence of sepsis increases with age and studies have described a 28-day mortality as high as 5% in older population following urinary tract infection with bacteremia (4,13). Other studies supporting these statements claim, that decline in antibiotic use may harm older populations who are already more likely to develop UTI related complications and bloodstream infections. They reported a significant increase of bloodstream infection and death within 60 days when antibiotic therapy was either not prescribed or deferred (4).

Our study should provide an overview of most common isolated organisms causing UTIs in older patient population in Split. Since this specific elderly sub-population is not commonly isolated addressed and evaluated from younger patient population guidelines addressing treatment of urinary tract infections, treatment suggestions require special attention and a more aggressive antibiotic treatment approach, as would be the case with younger patients. Our study also described local susceptibility rates of commonly encountered bacteria and may be of aid in choosing the appropriate antibacterial agent for empiric treatment initiation before narrowing down to antibiotic agents with known susceptibilities.

The main limitation of this study is its retrospective character. The medical records are prone to bias. Variables, as previous hospitalizations, comorbidities, risk factors which could help predict the risk of having multi-drug resistant organisms causing the UTI, could not be accurately distracted from patient records.

Another study limitation is the small sample size, even though etiology and resistance patterns were comparable with recent data about Croatia, published by the EARS-Net surveillance report.

6. CONCLUSION

In our patients, the most common isolated pathogen was *E.coli* with 50,5%, followed by *Proteus mirabilis* on second place with only 15%, and *Pseudomona aureginosae* on third place with 11,2%.

Antibiotic sensitivity of *E.coli* isolates was 94,1% to nitrofurantoin, making this agent a reliable first choice as empirical treatment for acute cystitis. Resistance rates over 10% to fluoroquinolones are precluding their use as first line agents for acute pyelonephritis and should hence not be empirically started, as long as sensitivity results are not established. Amoxicillin-clavulanic acid and all cephalosporin generations exhibited sensitivity over 75% and should be a preferred choice as first line. 100% sensitivity to carbapenems make this antibiotic a reliable choice of therapy, although it should be reserved for patients with severe course of infection or hospital acquired UTIs.

Even though overuse of antibiotics should be avoided and focused away from broad-spectrum therapies towards narrow-spectrum agents, empiric treatment of older patient population should include broad-spectrum antibiotic coverage before susceptibility results are available. The increased risk of UTI related complications and higher incidence of sepsis and mortality are reason enough to initiate therapy as soon as possible and cover a broad spectrum of very likely resistant organisms.

The importance of frequently updating information concerning native prevalence of antimicrobial resistance in uropathogens among local geographic regions cannot be enough emphasized, since it affects empiric treatment choice for urinary tract infections and antibiotic stewardship.

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8. SUMMARY

Objectives: To investigate the most common etiology of bacteria causing urinary tract infection (UTI) and their antibiotic sensitivity in older patients aged 65 years or above.

Materials and methods: From January 2018 until December 2018, 107 patients aged 65 years and above were treated for urinary tract infections at the Clinic of Infectology of the University Hospital in Split. We included patients with the diagnosis acute cystitis, prostatocystitis, acute cystopyelitis, acute pyelonephritis and urosepsis, which were diagnosed on the basis of clinical evaluation and laboratory diagnostics. The study was conducted as an observational retrospective study. Medical data were retrieved by reviewing the history of medical records stored in the archive of the Clinic of Infectology, University Hospital in Split.

Results: The largest number of patients (26,2%) were found in the age group 80 years and above. Urosepsis with 37,4% and pyelonephritis actua with 36,4% were the most frequent encountered diagnosis of patients with urinary tract infections treated in the Infectology department in 2018. *E.coli* (50,5%) was the most common isolated bacteria causing UTIs, in second place was *Proteus mirabilis* (15%), followed by *Pseudomonas aeruginosa* (11,2%), *Klebsiella pneumonia* (9,4%). *E.coli* resistance to ampicillin was the highest with 51,9%, followed by fluoroquinolones with 27,8%. High sensitivity to carbapenems with no isolated organsim resistant to it and to nitrofurantoin with 94,1% sensitivity was established. Almost all isolated bacteria in our study were showing sensitivity rates of over 80% to carbapenems.

Conclusions: The most common isolated pathogen causing urinary tract infection in older patients visiting the Clinic of Infectology in 2018 was *E.coli* with 50,5%. Sensitivity of *E.coli* was 100% to carbapenems, 94,1% to nitrofurantoin, and above 75% for amoxicillin-clavulanic acid, all 4 generations of cephalosporins and aminoglycosides. 27,8% resistance rate to fluoroquinolones preclude their use as first line agents for pyelonephritis, until antibiotic sensitivity has not been established. Nitrofurantoin represents an appropriate first-line agent to treat cystitis in our patient sample and carbapenems, 4th generation cephalosporins or amoxicillin-clavulanic acid should be considered as first-line agents for pyelonephritis.

9. CROATIAN SUMMARY

Naslov: Etiologija i antibiotska osjetljvost uzročnika infekcija mokraćnog sustava u bolesnika starije životne dobi liječenih tijekom 2018. godine u Klinici za infektologiju Kliničkog bolničkog centra Split.

Ciljevi: Istražiti najčešće bakterijske uzroničnike infekcija mokraćnog sustava i njihovu osjetljivost na antibiotike u starih bolesnika životne dobi od 65 i više godina.

Materijali i metode: Od siječnja do prosinca 2018.godine na Klinici za infektologiju Kliničkog bolničkog centra Split liječeno je 107 bolesnika u dobi od 65 i više godina zbog infekcije mokraćnog sustava (IMS). U istraživanje su uključeni bolesnici s dijagnozom akutnog cistitisa, akutnog pijelonefritisa i urospese. Dijagnoza se temeljila na kliničkoj evaluaciji i laboratorijskog dijagnostici. Istraživanje je provedeno kao opservacijska retrospektivna studija. Medicinski podaci dobiveni su pregledom povijesti bolesti pohranjenih u arhivi Klinike za infektologiju Kliničkog bolničkog centra Split

Rezultati: Najveći broj bolesnika (26,2%) bio je dobnoj skupini od 80 i više godina. U 2018. godini zbog IMS liječeno je nešto više ženskih (54,2%) nego muških bolesnika (45,8%) u dobi do 65 i više godina. Urosepsa sa 37,4% i akutni pijelonefritis sa 36,7% bile su najčešće dijagnoze. Najčeše izoliran uzročnik IMS bila je *E.coli* (50,5%), na drugom mjestu je bio *Proteus mirabilis* (15%), a potom *Pseudomonas aeruginosa* (11,2%) i *Klebsiella pneumonia* (9,4%). *E.coli* bila je najčešće rezistentna na ampicilin sa 51,9%, a potom na fluorokinolone sa 27,8%. Utvrđena je visoka osjetljivost *E.coli* na karbapeneme, bez ijednog rezistentnog izolata, te na nitrofurantoin na koji je bilo osjetljivo 94,1% izolata. Gotovo sve druge izolirane bakterije pokazale su osjetljivost na karbapeneme od preko 80%.

Zaključci: Sa 50,5% *E.coli* bila je najčešće izolirani uzročnik IMS u starijih bolesnika koji su 2018. godine liječeni na Klinici za infektologiju. Slijedili su je *P.mirabilis* sa 15% na drugom i *P.aeruginosa* sa 11,2% na trećem mjestu. Osjetljivost *E.coli* na karbapeneme bila je 100%, na nitrofurantoin 94,1%, te preko 75% na amoksicilin-klavulanat, na sve 4 generacije cefalosporina i na aminoglikozide. Rezistenija *E.coli* na flurokinolone od 27,8% isključuje ih kao antibiotike prvog izbora za pijelonefritis dok se ne utvrdi osjetljivost uzročnika na antibiotike. Srećom nitrofurantoin je odgovarajući lijek prvog izbora za liječenje cistitisa i u naših bolesnika. Pijelonefritis i urosepsa, infekcije koje su bile češće u našoj bolnici, trebalo bi empirijski liječiti amoksicilin-klavulanatom, trećom ili četvrtom generacijom

cefalosporina, ili u težoj prezentaciji bolesti karbapenemima kao poduzanim lijekvima prije nego se odredi antibiogram i prema njemu prilagodi terapija.

10. CURRICULUM VITAE

Personal Information:

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Education:

2013 -2019	Medical Studies in English, University of Split School of Medicine
2012	High School Diploma (A-level), Fichtenberg Oberschule, Berlin

Internships:

August to September 2015	Internship at Helios Klinikum Emil von Behring, Cardiology
May to June 2013	Internship at Krankenhaus Waldfriede, Gynecology
April to May 2013	Internship at Charite Benjamin Franklin, Gastroenterology
September 2012	Internship at Dr.med. Zeilinger, Gelenk- und Wirbelsaeulenzentrum Berlin, Neurosurgery

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