Universidade de Lisboa

Faculdade de Farmácia

Nosocomial and Community-Acquired Urinary Tract Infections

Catarina Gomes do Rosário Silva Martins

Monografia orientada pela Professora Doutora Isabel Portugal, Professora Auxiliar.

Mestrado Integrado em Ciências Farmacêuticas

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Resumo

No passado, acreditava-se que o trato urinário fosse um local estéril, onde a aquisição de bactérias era um fator disruptivo para o aparecimento de infeções do trato urinário. Estudos clínicos contradizem essa ideologia, confirmando a presença de um microbioma saudável, com mecanismos de defesa importantes.

As infeções do trato urinário são consideradas a segunda causa mais comum de doenças infeciosas, assumindo 40% de todas as infeções nosocomiais e a maioria das infeções adquiridas na comunidade. Importa reiterar que muitas destas são desenvolvidas em pacientes saudáveis, sem comorbilidades.

As repercussões financeiras das infeções do trato urinário são enormes, principalmente devido à sua elevada incidência. Dois exemplos, como a cistite e a pielonefrite, são os principais contribuintes para este problema de saúde. Os custos incluem prescrições de antibióticos, ausências laborais por doença, despesas de hospitalização, entre outos. Adicionalmente, o fator de recorrência acaba por avultar os custos associados a uma infeção urinária.

Um dos grandes problemas que surge é a crescente resistência antibiótica, uma vez que o tratamento usual das infeções urinárias exige este tipo de prescrição. O associado uso excessivo de antibióticos causa problemas preocupantes, não só para a segurança do paciente, como também para a comunidade envolvente. Desta forma, o médico deve não só questionar a gravidade da infeção, mas ainda, se existe benefício no tratamento antibiótico de um determinado paciente.

Para mudar o paradigma da resistência aos antibióticos estão a ser desenvolvidas novas estratégias de tratamento e medidas profiláticas. No entanto, existe ainda um longo caminho para ser percorrido, através da amplificação do número de estudos clínicos e do aprofundamento do conhecimento tanto do microbioma existente no trato urinário como das opções terapêuticas que dele podem resultar.

Palavras-chave: infeção nosocomial; infeção adquirida na comunidade; infeção do trato urinário; infeção recorrente; antibióticos.

Abstract

Formerly it was thought that the urinary tract was a sterile place, where the acquisition of bacteria was a disruptive factor for the appearance of urinary tract infections. Nowadays, the clinical studies contradict this ideology, confirming the presence of a healthy microbiome, with important defence mechanisms.

Urinary tract infections are considered the second most common cause of infectious diseases, assuming 40% of all infections acquired in the hospitals and the majority of community-acquired infections. It is noteworthy that many of these are developed in healthy patients, without comorbidities.

The financial implications of urinary tract infections are enormous, predominantly a result of its high incidence. Two examples of it, such as cystitis and pyelonephritis, are major contributors to the overall health burden. The costs include antimicrobial prescriptions, sick days, hospitalization expenses, among others. Furthermore, the recurrence factor ends up looming the costs associated with a urinary infection.

One of the big problems arising is the growing resistance to antibiotics, since the usual treatment of urinary infections requires antibiotic prescription. The associated antibiotic overuse causes serious problems, not only for the specific patient safety but for the surrounding community. Thus, the physician must question not only the state of the infection, but if there is benefit in a certain patient's antibiotic treatment.

To shift the paradigm of antibiotic resistance, new treatment strategies and prophylactic measures are emerging. However, there is still a long way to go, through the amplification of the number of clinical studies and the knowledge of both the microbiome existing in the urinary tract and the therapeutic options that may result from it.

Key words: nosocomial infection; community-acquired infection; urinary tract infections; recurrent infection; antibiotics.

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Abbreviations

SM - Smooth muscle

LUT - Lower urinary tract

GAG - Glycosaminoglycan

UTI - Urinary tract infection

UPEC - Uropathogenic *Escherichia coli*

ER - Estrogen receptors

PR - Progesterone receptor

RES - Reticuloendothelial system

CFU - Colony forming unit

PMNL - Polymorphonuclear leucocytes

HPF - High power field

ICU - Intensive care units

WHO - World Health Organization

CA-UTI - Catheter associated urinary tract infection

NUTI - Nosocomial urinary tract infection

MDR - Multidrug-resistant

rUTI - Recurrent urinary tract infections

GU - Gonorrhoeal urethritis

NGU - Non-gonorrhoeal urethritis

NAATs - Nucleic Acid Amplification Tests

EARS-Net - European Antimicrobial Resistance Surveillance Network

ECDC - European Center for Disease Prevention and Control

MRSA - Methicillin-resistant *Staphylococcus aureus*

PPCIRA - Program for the Prevention and Control of Infections and Antimicrobial Resistance

PBCI - Promotion of Basic Infection Control Precautions

PAPA - Antibiotic Prescription Support Program

INSA - National Institute of Health Doctor Ricardo Jorge

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1 Introduction

1.1 Urinary tract physiology

The urinary system can be divided into upper and lower compartments. While the upper compartment is comprised of the kidneys and ureters, the lower one contains the urinary bladder and urethra.(1,2) The urine flows from the kidneys through the ureters into the bladder, being finally eliminated by the urethra.(3)

The kidneys are surrounded by a protective capsule made of connective tissue. Each kidney is divided into an outer renal cortex and inner renal medulla and has approximately one million nephrons that are responsible for the filtration of the blood. In the meantime, the kidneys have five essential functions: regulation of water, inorganic ion balance and acid-base balance; removal of metabolic waste products and foreign chemicals from the blood and their excretion in the urine; gluconeogenesis and finally, production of different hormones/enzymes, such as erythropoietin and renin. After the three basic renal processes - glomerular filtration, tubular reabsorption and tubular secretion – the urine is complete and flows through the ureters to the bladder, propelled by contractions of the ureter wall smooth muscle.(4–8)

The bladder is surrounded by the detrusor, comprised by three layers of smooth muscle (SM) and is the compliant reservoir for urinary storage.(6) It is neurologically controlled, releasing urine when necessary and appropriate (micturition).(8) The detrusor plays a crucial role in this task, since the interactions occurring amongst the SM cells dictate the behaviour of the bladder wall – the basis of urinary continence involves relaxation of the detrusor and simultaneous contraction of the bladder neck. Interestingly, the bladder is thicker in men than women, as greater voiding pressure is needed to empty the bladder through the longer urethra of males.(1,4)

The luminal surface of the lower urinary tract (LUT), bladder, and proximal urethra, called the urothelium, is a transitional epithelium coated by a thin glycosaminoglycan (GAG) layer. Differentiated cells of the urothelium, umbrella cells, articulate an impermeable barrier between urinary waste products and underlying body tissues. Uroplakins, umbrella cell transmembrane proteins, contribute to the barrier function of the urothelium by forming dense plaques on the apical surface of the umbrella cells.(2,9) Besides this important barrier function, the urothelium represents a dual role

of "sensor-transducer" function answering to adjacent cells and mediate innate immune response to urinary tract infections (UTI). In males, the bladder neck is contiguous with the prostatic urethra. On the other hand, in females, both the bladder neck and urethra contact with the connective tissue of the anterior wall of the vagina, which allows it to be mobile but promotes a huge amount of stress (such as during childbirth) and can influence urinary continence.(1)

Finally, the urethra is the organ that presents the most evident differences between sexes. It is divided in anterior and posterior urethra. Although the female urethra has 3–4 cm in length, the male one is approximately 18–20 cm long and both are constituted by different types of cells, namely smooth and striated muscle fibers.(1,4,9)

The urinary tract is illustrated in Figure 1.

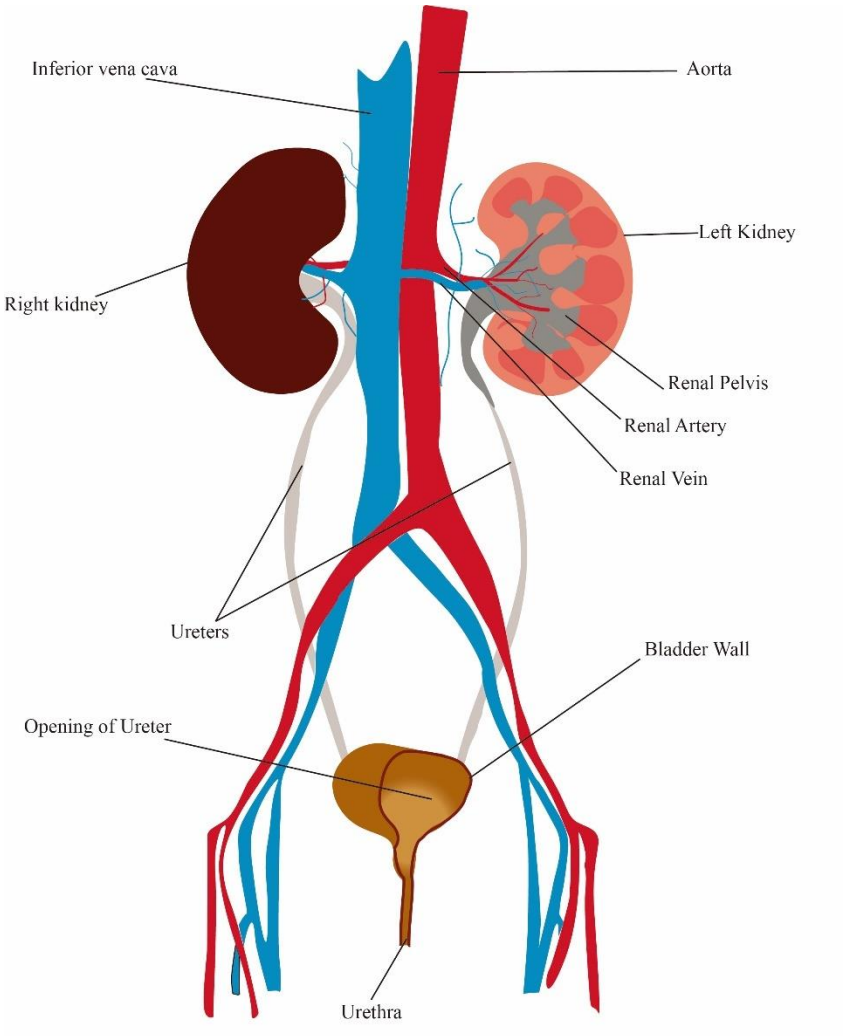

Figure 1. The physiology of the urinary tract. Adapted from (4,6,10)

1.2 Urinary tract microbiome

In order to understand the physiology and the role of the urinary system, it is essential to know its microbiome. Although, in the past, urine has been associated with sterility and the absence of organisms, we now know that this is not entirely true.(10–12) Studies have shown us that the use of next-generation sequencing and enhanced culture methods may detect communities of bacteria, fungi, and viruses (microbiota) in catheterized urine collected directly from the female bladder.(1,2) Thus, it confirms the fact that the urinary tract possesses its own protective microbiota and that its disruption results in LUT symptoms.(1) Urine pH varies among individuals and is usually acidic, although healthy urine pH can range from 5 to 8. It is composed of more than 2,600 compounds, including electrolytes, aminoacids, carbohydrates, between others. Given that many bacteria possess strictly aerobic or anaerobic metabolism, oxygen availability in the UT may play a role in shaping the ecology and spatial organization of the UT microbiota.(2)

The most detected bacteria in the bladders of adult women where the *Lactobacillus*, *Bifidobacterium*, *Gardnerella*, *Streptococcus*, and *Staphylococcus* while typical uropathogens such as uropathogenic *Escherichia coli* (UPEC) are rarely detected, except in women experiencing UTI symptoms. Live bacteria have also been detected in urine obtained by a catheter from older men which lead us to believe that the male bladder is probably not sterile either.(1) The mechanisms of the urinary microbiome-host relationship are still not quite understood. However, the proposals indicate that the natural human microbiome of the urinary tract enhances a protective effect and that it can change during the life cycle and seasonally, or with environmental changes (infection, treatments, diet, hormone state or lifestyle). (1,2,12)

In addition to its microbiome, the receptors for estrogen, progesterone and testosterone can be found in the urinary tract of both sexes across species, which may introduce us to their importance in development and maintenance of the urinary tract. Studies demonstrate that SM cells and lamina propria fibroblasts of the urethral wall had a high density of estrogen receptors (ERα and ERβ) and progesterone receptor (PR), both in female and male mice. The mechanism underlying the role of these type of hormones remains unknown, although the role of estrogen in regulating adrenergic receptors or its involvement in urothelial cell proliferation through different ER subtypes have been demonstrated.(1,13)

1.3 Most prevalent pathologies of the urinary tract

Pathologies of the urinary tract, namely in the kidneys, ureters, bladder and urethra, reduce the efficiency of the kidney's functions, disturbances in protein, acid-base solute and water homeostasis and excretion of the metabolic end-products. Thus, it is important to understand the different most prevalent diseases of the urinary tract and their impact in the human well-being and quality of life.(3,5)

To recognise this type of pathologies, it is necessary to study the most common and *major* manifestations of a urinary tract disease, such as:

- Abnormalities of the urine composition:
    - Proteinuria - the presence of protein in the urine.
    - Casts and cells – an indicator of inflammatory or degenerative changes in the kidney, where they are formed by agglomeration of desquamated cells and protein.
    - Hematuria – presence of intact blood cells in the urine.
    - Crystalluria – presence of crystals in the urine.
    - Pyuria - indicates an inflammatory exudation at any point of the urinary tract, usually renal pelvis and bladder. Pyuria is usually accompanied by the presence of bacteria in the urine.
    - Creatinuria - increased amount of creatinine in urine, due to excessive breakdown of muscular tissues. It is considered a good indicator for muscular dystrophy.
    - Hemoglobinuria - presence of hemoglobin in the urine. False hemoglobinuria occurs in cases of hematuria, when the red blood cells are destroyed and liberate their contents of hemoglobin into urine.
    - Glucosuria - the presence of glucose into the urine.
    - Among others.
- Abnormalities of the daily urine flow, such as:
    - Oliguria – the reduction in the daily urine output.
    - Anuria – the complete absence of urine.
    - Dysuria – the difficult or painful urination.
    - Stranguria – the slow and painful urination.

- Uremia - principal manifestation in renal failure. It is a syndrome caused mainly by the accumulation of urea and other ions in the blood.
- Rupture of the urinary bladder, renal pelvis and urethra.
- Defect in nervous control of the urination.
- Urachal leakage of urine.(5,14)

There are several pathologies in the urinary system that affect both men and women, such as: renal ischemia - reduction or decline of the blood flow through the kidneys, which is usually the result of circulatory failure(5), urinary tract infections that will be studied later, urinary incontinence - the uncontrollable and unreasonable loss of urine, whose incidence increases with age, being 50 times more likely in women thanks to the possibility of pregnancy and childbirth(15), glomerulonephritis which is an inflammation of the glomeruli (network of capillaries located at the beginning of a nephron in the kidney) that can come from an infection (bacterial or viral) or an immune disease, for example(16); nephritis – results from immune-mediated tubulointerstitial injury, initiated by medications, infection, and other causes, being one of the main causes of acute renal failure(14), urinary lithiasis – urinary calculi which are mostly compounded by calcium oxalate, calcium phosphate and uric acid, that can obstruct the urine flow(17), tumours of the bladder - quite common, being the fourth most frequent tumor in males, tumours of the kidneys - the most common malignant tumor of the renal parenchyma, associated with smoking and exposure to heavy metals for example(18), renal insufficiency - caused by the progressive decrease in kidney function, that affects more than two thousand new people every year in Portugal. If the degree of dysfunction is such that the person is not able to continue its normal life, it is said to be a state of renal failure and the clinical syndrome of uremia is manifested.(5,19)

2 Urinary tract infections

2.1 Pathogenesis

An UTI is a very frequent urological pathology, which appears in individuals of both sexes, in different age groups. It may occur by different ways: as a result of other underlying pathologies or predisposing factors or even in healthy individuals, who seem to have no reason to develop an infection.(18)

In practice, a urinary infection is defined as a ”microbial infiltration of the normally sterile urinary tract.”(10) This concept is based on the long-standing dogma that urine is sterile which, as discussed earlier, is false and can lead to impulsive pharmacotherapeutic decisions. A second common definition has emerged: “significant bacteriuria in a patient with symptoms or signs attributable to the urinary tract and no alternate source”, which seems more restrictive, although it does not define what symptoms or signs may be attributed to the urinary tract. Thence the diagnosis is confirmed (using the first definition) if bacteriuria is present and occurs when the pathogen is able to enter the urinary tract and reach more than a certain value of colonies/ml in urine (Table 1), when there is a wide variety of nonspecific symptoms. This ambiguity present on the definitions of UTIs certainly creates opportunities for overtreatment and can promote antibiotic overuse. (11,18,20)

Table 1. Microbiological diagnosis for different types of UTI.

Microbiological diagnostic			
	Asymptomatic bacteriuria	Cystitis & pyelonephritis	Urethritis
Common harvest route	Isolation of $\geq 10^5$ CFU/ml of the same bacterial strain in consecutive urine cultures obtained by urination (middle part of the stream) in the absence of symptoms.	Isolation of $\geq 10^3$ CFU/ml of bacteria in a urine culture obtained by urination (middle part of the stream).	≥ 5 polymorphonuclear leucocytes (PMNL) per high power field (HPF)
Another harvest route	Isolation of $\geq 10^2$ CFU/ml of bacteria in a urine culture obtained by sterile urinary catheter or sterile suprapubic puncture in the absence of symptoms (middle part of the stream) in the absence of symptoms.	Isolation of $\geq 10^2$ CFU/ml of bacteria in a urine culture obtained by sterile urinary catheter or suprapubic puncture.	The presence of ≥ 10 PMNL/HPF in the sediment from a spun first-void urine sample

Source: (11,18,20)

The most common cause of this pathology stands by the rise of microorganisms through the urethra, especially from enteric origin (for example, *Escherichia coli* and other *Enterobacteriaceae*). In a first phase, enterobacteria colonize the vestibule of the vulva and the periurethral region. Due to the proximity, the pathogens that contaminate the urethra and ascend to the bladder are commonly of intestinal origin. From these locations, a small number of bacteria ascend to the bladder and more exceptionally to the pelvis and renal parenchyma.(21)

Under normal circumstances, bacteria is eliminated by the flow and antibacterial properties of the urine and, to a lesser extent, by the presence of Immunoglobulin A (IgA) and the few polymorphonuclear cells present on the vesical surface. However, some specific factors of the bacteria or the host favours the colonization of the kidney, where the uropathogen ascends through the ureters.(18,21,22) The mucosal layer of the urothelium is consistently exposed to countless microbes, even though it is protected by various defence mechanisms such as micturition. Yet studies demonstrate that UPEC utilize the flow of urine (micturition) to extend adhesive surface appendages called pili to attach and secure themselves to the host epithelium. Fortunately the mucosa layer provides a secondary defence, inhibiting bacterial attachment to the mucosal wall.(1)

Recent evidence supports the existence of nonstructural contributors that make women more susceptible to UTI, largely due to the vulnerability caused by the reticuloendothelial system (RES), which provides the host with immunity against microbes.(1) This vulnerability may arise from the fact that most infiltrating monocytes differentiate into macrophages, which can impair adaptive immune responses to UTI, since they appear to inhibit the development of adaptive immunity to the bacteria.(23) The RES includes antigen-presenting cells also known as MHII+, macrophages, dendritic cells, CD11b+ and CD103+ cells and monocytes. A study presented results about the depletion of certain defence cells. The lack of monocytes had little effect on bacterial clearance, while the depletion of macrophages had no change for effecter cell infiltration or cytokine secretion, teasing however an increase in the number of dendritic cells. In addition, the absence of B and/or T cells severely impaired the defense of female bladders against UPEC. Another study showed and increased number of CD4+ and CD8+ cells in women affected by cystitis, suggesting these cells play a crucial role in the innate pathogenesis of the female bladder.(1)

On the other hand, there is the possibility of the colonization of the urinary tract by bacteria through other points of the organism, via hematogenous route. Hematogenous urinary tract infection is restricted to rarer microorganisms, such as *Staphylococcus aureus*, *Candida spp.*, *Salmonella spp.* and *Mycobacterium tuberculosis*.(18,22)

If bacteria is not eliminated, the colonization process will start (adhesion of the microorganism to the urothelium, reproduction and elimination through urine) or an infection (implying injury to the vesical epithelium) depending on the balance between the virulence of the bacteria, the size of the inoculum, local defensive mechanisms and the presence or not of anatomical or functional alterations of the urinary tract. If the inflammatory lesion of the bladder mucosa is not produced, an asymptomatic bacteriuria is produced.(21)

Through the incoming of microorganisms, it is possible that different types of urinary infections develop, which can be classified as lower (confined to the bladder, cystitis, or affecting the urethra, urethritis) or upper (related to the kidneys - pyelonephritis) and as either uncomplicated (occurring in a healthy host who has no structural or functional abnormalities, is not pregnant or who has not been instrumented with a catheter) or complicated (patients with impaired or obstructed urinary tract system or patients that use the medical devices).(20,24) The differentiation between complicated and uncomplicated UTI has implications for pre- and post-treatment assessment, type and duration of antimicrobial therapy and extent of urinary tract assessment.(25) Furthermore, the infection can progress through various levels of severity including asymptomatic bacteriuria, acute (including cystitis and pyelonephritis), chronic, and recurrent infection (the incidence of three or more UTIs per year, as well as 2 or more UTIs in less than 6 months), which is the *major* challenge in treatment of UTI patients.(20)

Bearing in mind that some of the symptoms of cystitis and pyelonephritis are similar, the diagnosis of the type of infection (lower or upper UTI) should be based on clinical examinations and laboratory results (Table 2).(20)

Table 2. Diagnostic evaluation for different types of UTIs.

<table>
<tr><th rowspan="2"></th><th colspan="3">Diagnostic evaluation</th></tr>
<tr><th>Cystitis</th><th>Pyelonephritis</th><th>Urethritis</th></tr>
<tr><td rowspan="8">Symptomatology</td><td rowspan="2">Dysuria</td><td>Fever (> 38°C)</td><td rowspan="2">Mucopurulent or purulent discharge</td></tr>
<tr><td>Chills</td></tr>
<tr><td>Frequency and urgency</td><td>Flank pain</td><td rowspan="2">Dysuria</td></tr>
<tr><td>Polyalkyuria</td><td>Nausea or vomiting</td></tr>
<tr><td>Absence of vaginal discharge</td><td>Costovertebral angle tenderness</td><td rowspan="4">Urethral pruritus</td></tr>
<tr><td>Suprapubic pain</td><td rowspan="3">With or without the typical symptoms of cystitis</td></tr>
<tr><td>Tenesmus</td></tr>
<tr><td>Absence of fever/low back pain/flank pain suggestive of pyelonephritis</td></tr>
<tr><td rowspan="2">Diagnostic measures</td><td rowspan="2">Urinalysis
(for example urine culture or dip stick testing)</td><td>Urinalysis with assessment of white and red blood cells and nitrite</td><td rowspan="2">Gram or methylene-blue stain of urethral secretions demonstrating inflammation</td></tr>
<tr><td>Urine culture and antimicrobial susceptibility</td></tr>
<tr><td>Urine culture is recommended in patients with atypical symptoms, as well as those who fail to respond to appropriate antimicrobial therapy and in pregnant women</td><td>Contrast enhanced computed tomography (CT) scan, or excretory urography
(if the patient remains febrile after 72 hours of treatment or immediately if there is deterioration in clinical status)</td><td>Positive leukocyte esterase test in first-void urine</td></tr>
</table>

Source: (4,15,20–22)

In Portugal, for the diagnosis of urinary tract infections, the most frequently used test is the reactive strip (39.9%). If the result turns out negative but the clinical suspicion of cystitis persists, 75% of the physicians who responded to the survey opt for the sediment and/or urine culture to confirm the diagnosis.(26)

Depending on the patient's conditions in which the urinary tract infection develops, we can differentiate between a nosocomial/healthcare-associated infection and a community-acquired infection. The first is an infection acquired when receiving treatment for a different illness at a healthcare facility or developing in a patient hospitaliazed for more than 48 hours before the onset of signs and symptoms consistent with the infection, while the last one matches an infection that is contracted outside of a healthcare setting or present at the time of admission.(26) Further ahead, this study will discuss the main differences present in an UTI from different sources.

2.2 Epidemiology

Urinary tract infection is one of the most prevalent infectious diseases (the second most frequent infectious process, being the most frequent bacterial infection in primary care(21)) in humans that can occur from childhood to old age, affecting both healthy and ill people.(27) It is considered the second most common cause of infectious diseases, accounting for approximately 40% of all the infections acquired in hospitals and 50% of bacteremia that can prolong the hospitalization. Thus, it is expected an increase in the morbidity and mortality rate in these patients.(20)

In the United States, about 11 million people affected with UTI have been annually referred to the healthcare centers and approximately 470,000 have been hospitalized, which annually costs was about $6 billion.(20) In Portugal, it is difficult to determine the real incidence of UTIs, being even more difficult to estimate the number of urinary infections in postmenopausal women. Clinical studies describe that, at 70 years of age, 15% of women have asymptomatic bacteriuria. This number increases to 30-40% in elderly women hospitalized or admitted to geriatric institutions and approximately to 100% in patients with permanent urinary catheters.(21)

In order to update data on uncomplicated UTI in women in clinical practice in Portugal, a questionnaire was carried out between April and May 2008 to a total of 148 general practitioners (86.3%) and urologists (13.7%). Most of the questionnaire was answered by men (56.8%), with a mean exercise time of 25.7 years. On average, each doctor consults 115 patients per week, with about 7.1 cases corresponding to consultations for urinary infections. Of the total number of cystitis diagnosed by the physician, 13.1% are complicated cystitis and 22.6% are recurrent urinary infections.(21)

In general, it is estimated that nearly half of the women and 12% of men will experience at least one UTI during their lifetime, with a quarter of these having a recurrence infection afterwards. Additionally, approximately one in three women will have had at least one episode of cystitis by the age of 24 years.(20,28) Thus, the prevalence varies in both sexes and in different age groups.(27)

In the first three months of life, UTI is more frequent in males due to structural changes such as the presence of posterior urethral valves. From that age onwards, UTI is more frequent in girls due to a functional cause (the reflux of urine, thanks to the incompetence of the vesicourethral valves), which spontaneously corrects itself with

puberty.(27) In boys, as in newborns, UTI can occur secondary to the presence of important structural changes that usually require surgical correction. Infection with *Staphylococcus aureus* is rare in children without in-dwelling catheters or other sources of infection, and coagulase-negative staphylococci and *Candida* spp. are associated with infections after instrumentation of the urinary tract. Early diagnosis is critical to preserve renal function of the growing kidney.(27,29)

From 15 to 50 years old, UTI is practically non-existent in men, while in women it has a prevalence that can reach up to 3% of the population(27) (young, sexually active women report incidence rates ranging from 0.5-0.7 per person-year, while age-matched men report an incidence rate of about 0.01 per person-year(2)). Such sex-related vulnerability is related to anatomical differences involving the female LUT. The female external urethra is near the entrance of the vagina, which houses large numbers of microbes. It is estimated that bacteria in the gut can migrate to the vagina and consequently to the urethra, evidenced by the prevalence of native intestinal flora that become uropathogens.(1) Furthermore, the fact that men have a longest urethra (farther apart from the anus) and the secretion of prostatic fluid, which have antibacterial activity, confirms the lower probability of developing urinary infections.(27)

Acute cystitis is extremely common among women of childbearing age, while acute pyelonephritis, much less common, is associated with high costs per episode and morbidity. In these cases, having sexual activity is a considerable risk factor.(21,27) While UTIs are very common among young, sexually active populations, the risk of developing this pathology increases with age, leading to an elevated risk in postmenopausal and elderly women, being the second most prevalent infection in this age group.(2) In both sexes, from the age of 50, anatomical (prostatic hypertrophy in men) and physiological (menopause in women) changes predispose to UTI. Many times chronic and often asymptomatic or tolerated locally and systemically to the point of being considered as a normal consequence of aging, which in most cases does not need antimicrobial treatment.(27)

On the other hand, the frequency of UTI increases during pregnancy and constitutes a risk for both mother (pyelonephritis, pre-eclampsia, eclampsia and hypertension) and fetus (prematurity, low birth weight and perinatal death). Twenty to forty percent of cases of asymptomatic bacteriuria associated with pregnancy progress to pyelonephritis

which can lead to kidney damage and fetal problems such as intrauterine growth retardation, prematurity, risk of perinatal death and congenital anomalies.(27)

For women with diabetes mellitus, UTIs occur more frequently and are more severe, causing complications that in other cases are rare.(30) Asymptomatic bacteriuria is common in diabetic people, especially in women. The proposed mechanism is the inhibition of phagocytosis by glycosuria and thus, the encouragement of bacterial adhesion. Diabetes mellitus increases the risk of acute pyelonephritis from *Enterobacteriaceae* infection. *Klebsiella* infection is particularly common.(27,31)

Speaking of numbers, together, cystitis and pyelonephritis are major contributors to the overall health burden and costs attributed to UTIs in women. The financial implications of UTI are enormous, predominantly aa a result of its high incidence. There are direct and indirect costs related to this pathology: outpatient doctor visits, antimicrobial prescriptions, sick days, hospitalization expenses, among others. The average duration of symptoms associated with acute UTI is about six days, with 2.4 days of activity restriction and 1.2 days of lost work time.(32)

Approximately 11.3 million women in the United States had ≥1 presumed acute community-acquired UTI resulting in antimicrobial therapy in 1995, with an estimated annual cost of community-acquired UTI of $1.6 billion. For nosocomial UTIs the annual cost is estimated of $424-$451 million, assuming a substantial overall medical burden.(2,33)

2.3 Nosocomial infections

Nosocomial infections are an important cause of mortality, especially in intensive care units (ICU), where patients are more fragile and immunocompromised. In developing countries, nosocomial infection is increasingly being recognized as a significant problem, not only because of the great health danger associated with the higher mortality, but also due to the economic burden of each day of hospitalization, as well as the expensive therapy required, often against resistant microorganisms.(34)

To realize the magnitude of the problem, one of the primary targets by the World Health Organization (WHO) is to discover and develop new antibiotics against resistant strains of Gram-negative bacteria such as carbapenem-resistant *Klebsiella pneumoniae*, *Acinetobacter baumannii* and *Pseudomonas aeruginosa*.(35,36)

Forty-eight to seventy-two hours after the patient's admission to the hospital the colonisation with resistant microorganisms begins and that is why taking appropriate isolation measures and monitor colonised patients with resistant microorganisms is crucial. Study articles show that one of the most effective measures against the proliferation of resistant microorganisms is to treat hospitalised patients in single rooms. By this method, healthcare workers pay more attention to hand hygiene compliance which leads to a decrease in the cross-transport of resistant microorganisms.(35,37)

Statistics demonstrate that up to 10% of all hospital patients develop nosocomial infection, revealing a third to be of urinary origin.(36,38) UTIs are the most common type of nosocomial infection accounting for 40% of all infections in hospitals and 34% in nursing homes. It is, in fact, a public health problem and a concern for the medical class.(35)

2.3.1 Pathophysiology and risk factors

Usually, the normal host defences against UTI are the unobstructed urethra, the voiding process and the normal bladder mucosa. One mechanism that will disrupt this line of defence is the insertion of a urinary catheter that unfortunately happens between 15 - 25% of admitted patients that stay 2-4 days. In hospitals, 80-90% of nosocomial UTIs

are associated with the use of urinary catheters (CA-UTI) and an additional 5-10% with other genitourinary manipulations.(28,36,38,39)

The insertion of a urinary catheter provides an easier access of uropathogens to reach the bladder and colonise the surface. After the colonisation, the attachment begins with the development of coating by biofilm, enhancing microbial adhesion and resulting in a nosocomial urinary tract infection (NUTI). The biofilm facilitates microbial adhesion to catheter surfaces which provides a stable and protective environment for microorganisms. Another risk of biofilm formation is catheter encrustation and catheter obstruction. Furthermore, the uroepithelial mucosa is damaged and there is an increase in residual urine bellow the catheter bulb, leading to new binding sites and perfect conditions for the bacterial proliferation.(28,36,38,39)

A catheter-associated UTI refers to UTIs occurring in a person whose urinary tract is currently catheterised or has been catheterised within the past 48 hours, with symptomatology concordant with fever, rigors, altered mental status, malaise, or lethargy with no other identified cause, flank pain, costovertebral angle tenderness, acute haematuria, pelvic discomfort and in those whose catheters have been removed dysuria, urgent or frequent urination and suprapubic pain or tenderness.(28)

As stated above, colonization with resistant microorganisms begins quickly after the patient is admitted to the hospital. CA-UTIs are often polymicrobial and caused by multiple-drug resistant uropathogens, being the leading cause of secondary healthcare-associated bacteraemia. Approximately 20% of hospital-acquired bacteraemias arise from the urinary tract and the mortality associated with this condition is approximately 10%. (28,40)

The most relevant risk factors for the occurrence of NUTI include the number of catheter insertions and the duration of catheterisation. Clinical studies indicate that the risk of NUTI rose from 19% for 5 days long catheterization to 50% for 14 days long catheterization.(36) Short-term catheterization usually identifies a catheter left in place for less than 7 days, while a “long-term” or “chronic” catheterization takes place for more than 28 days.(38) Also the existence of other comorbidities such as abnormalities of the urinary tract, chronic renal failure, diabetes mellitus, neurogenic bladder, patients with serum creatinine greater than 2 mg/dl or with fecal incontinence, can become more likely for the development of a NUTI. Age is another factor to be aware of, since elderly

population is more fragile and compromised. There is evidence that patients at high risk for CA-UTI were female, had a prolonged duration of catheterisation, had diabetes and had longer hospital and intensive care unit (ICU) stays.(28,40)

For the diagnosis it is necessary to identify a microbial growth of $\geq 10^2$ CFU/mL of one or more bacterial species in a single catheter urine specimen or in a mid-stream voided urine specimen from a patient whose catheter has been removed within the previous 48 hours.(28)

2.3.2 Main pathogens responsible

Gram-negative organisms predominate in hospital-acquired urinary tract infections, almost all of which are associated with urethral catheterization.(41) NUTIs can be caused by a greater spectrum of bacteria and fungi, when compared to community-acquired urinary tract infections. This variety depends on healthcare setting, geographical location and clinical environment.(34,42)

The most common pathogens are uropathogenic *Escherichia coli* (UPEC), being more frequent in community-acquired UTIs than NUTIs.(34) Then follows *Enterococcus faecalis*, *Klebsiella pneumoniae*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Proteus mirabilis*, *Enterobacter spp.*, *Serratia spp.* and *Candida spp.*. Many of these microorganisms are part of the patient's endogenous bowel flora, but they can also be acquired by cross-infection from other patients or hospital personnel. Contaminated solutions or non-sterile equipment are also a source of risk for contracting a nosocomial infection.(2,24,38,43,44) It should also be noted that in patients with diabetes mellitus, infections caused by *Klebsiella pneumoniae*, Enterobacter spp., and Candida spp. are more common, due to immunological impairment.(34,45)

2.3.3 Preventive measures

The knowledge of the pathobiology of NUTI and its risk factors is crucial to the prevention of this condition, since hospital infection control programs can prevent up to 33% of nosocomial infections including the urinary one. Thus, it is crucial to firstly geographically focalize differences in microorganisms and their resistance and, secondly, to allow global metanalysis and best practice guidelines. (36–38)

The use of urinary catheters is the *major* risk factor for the development of these infections. A controlled catheter policy including shorter duration of catheter use and more attention to catheter hygiene can modify the percentages of patients suffering of this disease and consequently increase their average life expectancy. Patients with asymptomatic bacteriuria can generally be treated initially with catheter removal/exchange and do not necessarily require antimicrobial therapy, meanwhile symptomatic patients should receive antibiotic therapy.(36–38)

2.4 Community-acquired infections

A community-acquired infection was defined as an infection contracted outside of a health care facility or an infection present at the time of admission.(26) Most of the community-acquired infections are related to uncomplicated UTIs which are commonly found in patients with a healthy urinary tract system and without using medical devices.(20)

UTI was designated as the most common bacterial infection encountered in the ambulatory care setting in the United States, accounting for 8.6 million visits (84% by women) in 2007. Statistics state that by the age of 32 years, half of all women report having had at least 1 urinary tract infection.(46)

Community-acquired uncomplicated UTIs account for a large proportion of infectious diseases in females and a substantial amount of oral antibiotics is prescribed daily to treat these infections. The uncomplicated infections include the acute, sporadic or recurrent cystitis and/or pyelonephritis (less common), limited to non-pregnant women with no known relevant anatomical and functional abnormalities within the urinary tract or comorbidities.(28,47)

Lastly, especially in this type of infections, it is crucial to understand the resistance patterns of the different communities to implement the most appropriate therapy.

2.4.1 Pathophysiology and risk factors

As previously explained, UTI is commonly caused by bacteria from the patient's own intestinal flora that enter the urinary tract upwards through the urethra. Women are more likely to experience uncomplicated community-acquired UTIs than men, due to their higher rates of bacterial colonization of the urethral and periurethral body sites. The ascension of bacteria and bladder establishment is facilitated by the shorter urethra, what favours the infection in this population. Curiously while community-acquired UTIs are more common among females, the rate of mortality from complicated UTI and pyelonephritis is higher in males.(48)

In women, vaginal colonization is a prerequisite for bladder infection. This colonization depends on the volume of the inoculum, bacterial virulence factors (bacterial adhesins such as Pili type 1 or Pili P, which facilitate adherence to the urothelium) and failure of

defence mechanisms (such as normal urinary flow, continuous exfoliation of the urothelium and the usual flora of the vaginal opening).(49) Changes in the vaginal microflora play a critical role in facilitating vaginal colonization with coliforms, such as alterations in the concentration of lactobacilli, especially hydrogen peroxide producing strains.(32)

Generally, the factors that predispose to vaginal colonization also predispose to bladder colonization and infection. Thereby, the risk factors that increase susceptibility to UTI commonly include female sex, intestinal or vaginal changes, sexual intercourse, new sexual partner, use of spermicides, contraceptives, a mother with a history of UTI, a history of UTI during childhood and previous antibiotic use.(28,44,46,48)

2.4.2 Main pathogens responsible

In women, UPEC causes 75-95% of episodes of uncomplicated, community-acquired cystitis and pyelonephritis. The remaining cases are mostly caused by *Proteus mirabilis, Staphylococcus saprophyticus* and *Klebsiella pneumoniae*. *Proteus spp*. is frequently founded among people with 50 years or more, unlike *S. saprophyticus*. (26,28,34,44,46,48,50)

Although rarer in community-acquired infections, in complicated infections the spectrum of bacteria is broader than in uncomplicated UTI and bacteria are likely more resistant to antimicrobials. UPEC is responsible for 70% of complicated community-acquired UTI cases and 66% of complicated UTI cases or acute pyelonephritis. Follows *Enterecoccus spp., K. pneumoniae, Candida spp., S. aureus, P. mirabilis, P. aeruginosa* and *S.agalactiae.* (32,34)

A study which aimed to understand the risk factors of multidrug-resistant (MDR) bacteria that caused community-acquired UTI demonstrate that *E.coli* was mainly responsible for UTIs in females (76.4 %), followed by *Klebsiella spp.* (12.2 %) and *Pseudomonas spp*. (4.9 %). Among males, 61.5% of isolated bacteria was *E.coli* while 17.9% was *Klebsiella spp*.. It was concluded that the incidence of *E. coli* was statistically higher in females than in males.(50)

Although UPEC strains are the most prevalent causative agent of UTIs, not all have the same ability to infect the urinary tract. Only strains with a certain degree of virulence

can produce an infection in patients with an intact urinary tract.(20,21) Among the main virulence factors of *E. coli*, the following stand out:

- the presence of adhesins that allow its adhesion to the urothelium;

- the ability to structure itself into biofilms;

- the release of toxins;

- the presence of invasins or other elements such as pathogenicity islands.

The more virulence factors compete in an *E. coli* strain, the more virulent it is. Against these mechanisms, the host has different lines of defence that will stimulate the immune system.(20,21)

2.4.3 Preventive measures

After treatment for uncomplicated cystitis or pyelonephritis, a urine culture is unnecessary if symptoms have resolved, except in pregnant women (for whom treatment of persistent asymptomatic bacteriuria is recommended).(28)

To prevent a community-acquired UTI, behavioural and personal hygiene measures can be taken into account daily, in order to reduce the chances of microbial colonization of the urinary tract. Measures for preventing this type of infections are listed in the next chapter that approaches recurrent infections.

2.5 Recurrent infections

The term is relatively recent, being generally accepted for the first time in 2000. Over time and with the evolution of research in recurrent urinary infections, its definition reached as “three episodes of urine culture positive UTI in the previous 12 months or two episodes within the 6 months”.(51,52) In healthy women, an acute UTI leads to a 25-50% chances of a recurrent urinary tract infection (rUTI) within months of the initial infection, many times by the same bacteriological strain.(48)

Although common, the pathobiology of rUTI is not completely understood, with two models of infection development being acceptable: repeated ascending infections from a reservoir outside the urinary tract (such as the gut) or reemergence from a persistent population residing within the urinary tract.(28,52)

One of the examples was demonstrated in 2017 through a study with transient exposures to the vaginal microbiota, particularly *Gardnerella vaginalis*. The study demonstrated that this can arouse quiescent UPEC reservoirs, leading to bladder lumen reinoculation, epithelial cell death and exfoliation, and kidney damage.(48,53) Epidemiological studies confirm this possibility, showing that the bacteria responsible for recurrent infections are identical to those who caused the initial infection in 68% of cases. From these facts it has been suggested that more penetrating antibiotics could better eliminate bacterial reservoirs from the bladder and consequently reduce the incidence of chronic and recurrent UTI.(54)

Identifying the origin and the biological method that trigger the reemergence of persistent bacterial populations within the urinary tract is essential to understand the pathogenesis of rUTIs and to adequately and definitively treat the pathology.

Recurrent infections are classified, according to pathogenesis, into relapses or reinfections. These are due to new infections caused by the same strain, within 2 weeks after the end of antibiotic therapy (usually due to inadequate antibiotic therapy, antibiotic resistance or some underlying change in the urinary tract), or a different one, occurring two weeks after the end of the initial UTI treatment, in a patient who was cured.(27,51) Generally, the etiologic agent of recurrent UTI is *E. coli*. However, in rUTI, antibiotic treatment must be based on pre-treatment uroculture, and cure must be proven with post-antibiotherapy uroculture.(51)

The disease can be modelled by an oscillating pattern of relapsed infection interspersed with periods of remission between infections, interfering with the patients' daily well-being. The risk factors usually associated with the recurrence of urinary infections are as follows(28,52,55):

For young and pre-menopausal women

- Sexual intercourse;
- Use of diaphragm, spermicide and exposure to oral contraceptives;
- A new sexual partner;
- A mother with a history of UTI;
- History of UTI during childhood;
- Blood group antigen secretory status.

For post-menopausal and elderly women

- History of UTI before menopause;
- Urinary incontinence;
- Atrophic vaginitis due to oestrogen deficiency;
- Cystocele;
- Increased post-void urine volume;
- Blood group antigen secretory status;
- Urine catheterisation and functional status deterioration in elderly institutionalised women.

For this last group, estrogen levels also seem to play an important role. When reduced, the vaginal pH increase, endogenous vaginal microflora decrease and the incidence of prolapse due to muscle weakness is increased. Each of these factors may predispose women to pathogenic *E. coli* colonization and studies indicate that they can promote a delayed development of the protective bladder GAG layer, increasing susceptibility to bacterial colonization and intracellular bacterial community formation.(13,52)

The diagnosis of rUTI should be confirmed by urine culture, being an extensive routine workup (including cystoscopy, imaging, among other), not routinely recommended (only in more severe cases, such as suspected renal calculi) as the diagnostic yield is low.(28) The levels that determine a rUTI are $\geq 10^3$colonies/ml.(56)

For the prevention of rUTIs, it is fulcral to be aware of the urological risk factors that may be triggering this recurrence. Thus, the interventions to be taken are, in order: avoidance of risk factors, non-antimicrobial measures and antimicrobial prophylaxis.(28) A number of behavioral and personal hygiene measures (such as reduced fluid intake, habitual and post-coital delayed urination, wiping from back to front after defecation, douching and wearing occlusive underwear) have been suggested to increase the risk of rUTI. However, studies demonstrate that none of these plausible behavioral factors were shown to significantly increase the risk of rUTI.(46,52)

Pharmacological therapy for the treatment of a recurrent urinary infection moves towards the usual therapy for an acute infection, being beneficial to act previously, through the prophylaxis of the pathology. The following table (Table 3) illustrates several prophylactic therapies that may be considered.(20,27,28,46,49,55,57)

Table 3. Prophylactic therapies for women suffering from recurrent UTIs.

	Prophylaxis method	Prophylactic therapy	Evidence level
Non-Antimicrobial	Hormonal replacement	Vaginal oestrogen replacement for post-menopausal women. Restores the vaginal pH and therefore suppresses gram negative bacterial growth.	Weak
	Immunoactive prophylaxis	*Escherichia coli* (OM-89) – Uro-Vaxom®, for all age groups of female patients. Reduces the rate of infectious recurrences by 39%.	Strong
	Prophylaxis with probiotics	Use of *Lactobacillus rhamnosus* GR-1 and *Lactobacillus reuteri* RC-14. Probiotics can be given as oral lactobacillus administration or vaginal.	Weak
	Prophylaxis with cranberry	Intake of cranberry juice, tablets, syrup, capsules or fruit powder. The active principle - type A proanthocyanidin – has an inhibitory effect on motility of *Pseudomonas aeruginosa*, *Escherichia coli* and *Proteus mirabilis*, as well as their anti-adherence effect.	Weak
	Prophylaxis with D-mannose	2g per day was significantly superior to placebo and as effective as 50mg nitrofurantoin in preventing rUTI. D-Mannose is a monosaccharide that is easily absorbed and excreted in the urine and can prevent the adhesion of bacteria, especially *E. coli* to the uroepithelial cells.	Medium
	Endovesical instillation	Endovesical instillations of hyaluronic acid and chondroitin sulphate have been used for GAG layer replenishment in the treatment of interstitial cystitis, overactive bladder, radiation cystitis and for prevention of rUTI.	Medium
Anti-microbial	Continuous low-dose antimicrobial** and post-coital prophylaxis	Antimicrobials may be given as continuous low-dose prophylaxis for longer periods (3-6 months) or as post-coital prophylaxis, both regimens reduce the rate of rUTI. Regimens include: • nitrofurantoin 50mg or 100mg once daily; • fosfomycin trometamol 3g every ten days; • trimethoprim 100mg once daily; • during pregnancy*** - cephalexin 125mg or 250mg or cefaclor 250mg once daily.	Strong
	Self-diagnosis and self-treatment	In patients with good compliance, self-diagnosis and self-treatment with a short course regimen of an antimicrobial agent should be considered. The choice of antimicrobials is the same as for sporadic acute uncomplicated UTI.	Strong

Source: (20,27,28,46,49,57)

**Its suspension leads to 60% of patients having a new infection within 3-4 months.

*** Post-coital prophylaxis should be considered in pregnant women with a history of frequent UTIs before onset of pregnancy, to reduce their risk of UTI.

Finally, the development of vaccines composed of whole bacteria, fimbriated bacteria elaborated from infecting microorganisms themselves (autovaccines) or with subcellular components (fimbriae/adhesins) has been one of the main targets for the prophylaxis of rUTI.(27) Uro-vaxom® is already largely used, avoiding unnecessary treatment with antibiotics and improving prevention against recurrence. *In vitro* and *in vivo* studies in animals and humans have shown that this preparation triggers a series of immunopharmacological effects - increases the metabolic and functional activities of lymphocytes and macrophages and the levels of urinary and intestinal secretory IgA.(22,39,47,57,58)

With the progress of science, many other vaccines have been created, namely the Uro-Vac® (a vaginal mucosal vaccine) with strains of *E.coli, Proteus mirabilis, Klebsiella pneumoniae, Morganella morganii* and *Enterococcus faecalis* inoculated or the Uromune® (sublingual spray) this time with inoculated *E.coli, Klebsiella pneumoniae*, *Proteus vulgaris* and *Enterococcus faecalis* strains.(22,39) Studies revealed that Uromune® could effectively reduce the UTI recurrence rate and improve the quality of life in frail institutionalized older adults.(59)

The main goal of the use of vaccines is to improve the immune defences in the urogenital tract mucosa, prevent bacterial adherence and thus colonization in the region of the vagina and urethra. In addition of being a method that will certainly reduce the mortality rate, it will also reduce economic costs. Different vaccines based on the whole cells (killed or live-attenuated vaccines) and antigens (subunits, toxins and conjugated vaccines) have been evaluated against UTIs pathogens, although none has proven to be ideal.(20,55)

2.6 Pharmacological and non-pharmacological therapies

We conclude from the information previously provided that the knowledge of the spectrum and susceptibility profile of the uropathogens is crucial for an effective treatment. Thus, therapeutic decisions should be based on this information as well as in other criteria such as the efficacy for the particular indication in clinical studies, tolerability and adverse reactions, adverse ecological effects, costs and availability.(28,41,55)

It is increasingly important for the therapeutic choice to be as specific and individual as possible, on the basis of the patient's allergy and compliance history, local practice patterns, the prevalence of resistance in the local community (if known), in order to decrease the chances of antibiotic resistance. Thresholds are suggested for the prevalence of resistance in a community above which a drug is not recommended (20% for trimethoprim–sulfamethoxazole and 10% for fluoroquinolones). Hereupon, the choice of regimen has become more complicated as antimicrobial resistance among the bacterial strains increases worldwide.(46)

The classification of the antibiotics is based on their mechanism of action. Antibiotics can inhibit protein synthesis (aminoglycosides, chloramphenicol, macrolides, streptomycin and tetracycline), interact with DNA and RNA synthesis (quinolones and rifampicin), inhibit synthesis or damage the bacterial wall (β-lactams and glycopeptides) or modify the energy metabolism of the microbial cell (sulfonamides and trimethoprim).(32)

Surprisingly, some authors argue that the benefit of treating all symptomatic UTIs is limited. In cystitis, the primary objective is to improve the patient's symptoms, which are often self-limited, of brief duration, and only slightly shortened by antibiotic treatment. The generally benign (other than symptoms) nature of "symptomatic UTI" is suggested by the billions of people around the world who have suffered "UTI" without access to antibiotics and have fully recovered.(24,60)

The following chapters intend to demonstrate the most recommended therapies for different types of urinary tract infections.

2.6.1 Uncomplicated cystitis

The most common uncomplicated UTI is cystitis, manifesting itself mainly among women. Its characteristics, usually mild and associated with an absence of complications, meant that therapeutic decision-making was generally empirical. However, despite the positive prognosis relatively simple and quick treatment, a conscious and informed therapeutic consideration (Table 4) is crucial for the health's patient.(21,57)

Table 4. Pharmacological therapies for uncomplicated cystitis.

	Pharmacological therapy	Dosage and duration of treatment
Firstline treatment	Fosfomycin trometamol	3g single dose
	Pivmecillinam	400mg three times a day for 3-5 days
	Nitrofurantoin (such as nitrofurantoin monohydrate/macrocrystals)	100mg twice daily for 5 days
Alternative antimicrobials	Trimethoprim alone or combined with a sulphonamide (such as sulfamethoxazole)	Alone: 200mg twice daily for 3 days TMP-SMX: 160mg and 800mg twice daily for 3 days
	Cotrimoxazole	160/800mg twice daily for 3 days
	Trimethoprim	200mg twice daily for 5 days

Source: European Association of Urology's guidelines.

Because of worldwide high *E.coli* resistance and negative ecological effects, aminopenicillins are no longer suitable for empirical therapy. In this type of UTI, fluoroquinolones should only be used when it is considered inappropriate to use recommended antibacterial agents.(28,48)

For pregnant women penicillins, cephalosporins, fosfomycin, nitrofurantoin (not in case of glucose-6-phosphate dehydrogenase deficiency and during the end of pregnancy), trimethoprim (not in the first trimester) and sulphonamides (not in the last trimester), can be considered.(28)

Lastly, cystitis without involvement of the prostate is uncommon in men and therefore, should be classified as a complicated infection. Thus, for the vast majority, it is important to choose a treatment with antimicrobials penetrating into the prostate tissue,

such as seven days of TMP-SMX or a fluoroquinolone if in accordance with susceptibility testing.(28)

If the symptoms persist after the treatment and in those whose symptoms resolve but recur within two weeks, urine culture and antimicrobial susceptibility testing should be performed. Retreatment with a seven-day regimen using another agent should be considered, assuming that the infecting organism is not susceptible to the agent originally used.(61)

2.6.2 Uncomplicated pyelonephritis

The guidelines recommend the treatment of patients with uncomplicated pyelonephritis not requiring hospitalisation with a short course fluoroquinolones as first-line treatment. Meanwhile for the hospitalised ones, the initial treatment must include an intravenous antimicrobial regimen (Table 5). For those who improve clinically and can tolerate oral fluids, a switch for oral antimicrobial therapy must be done.(28)

Table 5. Pharmacological therapies for uncomplicated pyelonephritis.

	Pharmacological therapy	Dosage and duration of treatment
Empirical oral therapy	Ciprofloxacin	500-750mg twice daily for 7 days
	Levofloxacin	750mg per day for 5 days
	Trimethoprim sulfamethoxazol	160/800mg twice daily for 14 days
	Cefpodoxime	200mg twice daily for 10 days
Empirical parenteral therapy	Ciprofloxacin	400mg twice daily
	Levofloxacin	750mg every day
	Ceftriaxone	1-2g every day

Source: European Association of Urology's guidelines.

As second-line empirical parenteral therapy are for example cefepime and piperacillin/tazobactam, being last-line alternatives (used in multi-drug resistant organisms) imipenem/cilastatin, meropenem, ceftolozane/tazobactam, among others.(28)

2.6.3 Complicated UTIs

Complicated UTIs are associated with a greater spectrum when compared to uncomplicated UTIs. (42,62) Furthermore the bacteria are more likely to be resistant. This type of infection is related to men, pregnant women, people with comorbilities such as diabetes, patients with relevant anatomical or functional abnormalities of the urinary tract, indwelling urinary catheters or renal diseases.(28,34) The treatment for complicated UTIs (Table 6) should be as specific as possible, with dosages calculated according to the patient's characteristics.

Table 6. Pharmacological therapies for complicated UTIs.

	Pharmacological therapy	Duration of treatment
Firstline treatment	Amoxicilin plus an aminoglycoside	Treatment for 7-14 days (14 days when prostatitis cannot be excluded). If the patient is afebrile and hemodynamically stable for at least 48 hours, it must be considered the shorter treatment.
	2nd generation cephalosporin plus an aminoglycoside	
	3rd generation cephalosporin IV (for complicated UTI with systemic symptoms)	
Only if local resistance is < 10%	Ciprofloxacin (must not be used in patients who have used in the last six months)	

Source: European Association of Urology's guidelines.

2.6.4 Catheter-associated UTIs

Catheter-associated UTIs are associated with complicated infections, following the treatment described above. The recommendations for the management of the disease include:(28,63,64)

- Shorter duration of catheterisation.
- Hydrophilic coated catheters use.
- Urine culture prior to initiating antimicrobial therapy in catheterised patients in whom the catheter has been removed.

- No treatment for catheter-associated asymptomatic bacteriuria in general.
- Treatment of catheter-associated asymptomatic bacteriuria prior to traumatic urinary tract interventions.
- Replacement/Removal of the indwelling catheter before starting antimicrobial therapy.
- Unuse of topical antiseptics or antimicrobials to the catheter, urethra or meatus.
- Unuse of prophylactic antimicrobials to prevent CA-UTIs.

2.6.5 Urethritis

Urethritis can be of either infectious or non-infectious origin, being typically spread by sexual contact. The gonorrhoeal urethritis (GU) is usually caused by *Neisseria gonorrhoeae* (Table 7), while the non-gonococcal urethritis (NGU) results from a wider diversity of microorganisms such as *Chlamydia trachomatis* (Table 9) (11-50%), *Mycoplasma genitalium* (Table 10) (6-50%), *Ureaplasma urealyticum* (Table 11) (5-26%), *Trichomonas vaginalis* (Table 12) (1-20%) and adenoviruses (2-4%).(28,65)

For severe urethritis empirical treatment (Table 8) should be started following diagnosis. On the other hand, if the patients symptoms are mild, delayed treatment guided by the results of Nucleic Acid Amplification Tests (NAATs) is recommended.(28,66)

Table 7. Pharmacological therapy for gonorrhoeal urethritis (*Neisseria gonorrhoeae*)

	Pharmacological therapy	Dosage and duration of treatment
Firstline treatment	Ceftriaxone	1g IM or IV single dose
	Azithromycin	1g p.o. single dose
Firstline treatment	Cefixime + Azithromycin	400mg p.o. + 1g p.o. single dose
	Gentamicin + Azithromycin (for example, if cephalosporin allergy)	240mg IM + 2g p.o. single dose
	Doxycycline (if azithromycin allergy cephalosporin allergy)	100mg p.o. twice daily for 7 days

Source: European Association of Urology's guidelines.

Gonorrhoea is often accompanied by chlamydia infection, so anti-chlamydia therapy should be added in patients suffering from GU.(66)

Table 8. Pharmacological therapy for non-gonorrhoeal urethritis with a non-identified pathogen.

Non-identified pathogen		
Firstline treatment	**Pharmacological therapy**	**Dosage and duration of treatment**
	Doxycycline	100mg p.o. twice daily for 7 days
Alternative antimicrobials	Azithromycin	500mg p.o in day 1, 250mg p.o. for 4 days

Source: European Association of Urology's guidelines.

Table 9. Pharmacological therapy for non-gonorrhoeal urethritis with *Chlamydia trachomatis*.

Chlamydia trachomatis		
Firstline treatment	**Pharmacological therapy**	**Dosage and duration of treatment**
	Azithromycin or doxycycline	1.0-1.5g p.o. single dose 100mg p.o. twice daily for 7 days
Alternative antimicrobials	Levofloxacin	500mg p.o. every day for 7 days
	Ofloxacin	200mg p.o. twice daily for 7 days

Source: European Association of Urology's guidelines.

Table 10. Pharmacological therapy for non-gonorrhoeal urethritis with *Mycoplasma genitalium*.

Mycoplasma genitalium		
Firstline treatment	**Pharmacological therapy**	**Dosage and duration of treatment**
	Azithromycin	500mg p.o in day 1, 250mg p.o. for 4 days
Alternative antimicrobials	Moxifloxacin (in case of macrolide resistance)	400mg every day for 7-14 days

Source: European Association of Urology's guidelines.

Table 11. Pharmacological therapy for non-gonorrhoeal urethritis with *Ureaplasma urealyticum*.

Ureaplasma urealyticum		
Firstline treatment	**Pharmacological therapy**	**Dosage and duration of treatment**
	Doxycycline	100mg p.o. twice daily for 7 days
Alternative antimicrobials	Azithromycin	1.0-1.5g p.o. single dose

Source: European Association of Urology's guidelines.

Table 12. Pharmacological therapy for non-gonorrhoeal urethritis with *Trichomonas vaginalis*.

Trichomonas vaginalis		
Firstline treatment	**Pharmacological therapy**	**Dosage and duration of treatment**
	Metronidazole or tinidazole	2g p.o. single dose
Alternative antimicrobials	Metronidazole	500mg p.o. twice daily for 7 days

Source: European Association of Urology's guidelines.

If persistent non-gonococcal urethritis, the doctor must review the therapy and choose a therapeutic combination relevant to the specific case.

2.6.6 Non-pharmacological therapies

All symptomatic ITU must be treated using antibiotic therapies, depending on the bacteria found and local resistance patterns.(1,54,67) Non-pharmacological therapy involves the adoption of preventive measures and symptom relief, in addition to pharmacological treatment. Among the measures to be adopted, the following stand out: wear cotton clothes or light fabrics, clean from front to back towards the anus, avoid holding the urine for a long time, drink at least 1.5L of water, change the intimate absorbent with frequency, urinate after sexual intercourse, avoid excessive intimate hygiene, bathing or vaginal showers.(52)

2.7 Antibiotic resistance

Nowadays, treatments for UTI and rUTI rely primarily on antibiotic therapy to eliminate the pathogen and achieve the so desired UT sterility.(68) Despite the studies that confirm the existence of the urinary microbiome, conventional antimicrobial strategies for treating UTIs yet do not include the preservation or restoration of the microbial community that exists in the host healthy state. However, the microbial communities that reside in many body sites are known to play critical roles in preserving host physiology and health.(2)

UTIs became more difficult to treat from 1999 to 2010 according to the Drug Resistance Index, with this trend being attributed to increasing antibiotic resistance.(48) In the last years, European countries have been a place of great variations in microbial sensitivity to different antibiotics, revealing a progressive emergence of resistance to fluoroquinolones and other antibiotics commonly used in the empirical treatment of community UTIs. *E.coli*, the most prevalent uropathogen, has high resistance to commonly used antibiotics such as amoxicillin and trimethoprim-sulfamethoxazole.(67)

One example of a general antibiotic resistance phenotype is ST131, which represents a group of strains of extraintestinal *E. coli* exhibiting multidrug resistance. These strains exhibit resistance to beta-lactams and fluoroquinolones and, indeed, seem to be driving antibiotic resistance globally while causing, among other infections, UTIs and bacteremia.(69,70)

The progressive elimination of susceptible strains to the most used antibiotics and the consequent selection of resistant ones is a natural and expected process, being enhanced by the frequently inappropriate use of antimicrobials. In practice, the increase in resistance rates means that, when faced with an infection caused by a certain microorganism, this one is more likely to be resistant to commonly used antibiotics, with the infection being only treatable by broader-spectrum drugs, with greater potential for generating resistance.(71) Thus, to effectively treat UTI patients, knowledge of the local bacterial epidemiology and its pattern of resistance is important. It is imperative that clinicians are constantly updated on local resistance profiles in order to update empirical antimicrobial therapy regimens.(32)

Bacteria became resistant to antimicrobials through several mechanisms:

- Changes in bacterial cell wall permeability, which restricts the access of antimicrobials to target sites;
- Active efflux of the antibiotic from the microbial cell;
- Enzymatic modification of the antibiotic;
- Degradation of the antimicrobial agent;
- Acquisition of alternative metabolic pathways to those inhibited by the drug;
- Modification of antibiotic targets;
- Overproduction of the target enzyme.(72)

The national network collaborates with the european antimicrobial resistance epidemiological surveillance network, annually sending data representative of the portuguese reality to the European Antimicrobial Resistance Surveillance Network (EARS-Net), coordinated by the European Center for Disease Prevention and Control (ECDC).(71)

According to data from the ESAC-Net, the global consumption of antibacterials in Portugal in primary care remains at a still high level (21.6), although below the average of the Europe (21.9) (expressed in DHD - defined daily doses per thousand inhabitants per day). In hospitals, the average is 1.58 in Portugal and 2.06 in Europe. When analysing the consumption of antibacterials by classes in hospitals in Portugal and Europe, penicillins stand out, followed by cephalosporins/other beta-lactams, macrolides, lincosamides and streptogramins and quinolones, followed by cephalosporins and other classes.(71)

In Portugal, the percentage of methicillin-resistant *Staphylococcus aureus* (MRSA) has been decreasing since 2011 (54.6%). In 2016, this value was 43.6%, showing a 20% reduction. The main reasons for this decline are based not only on the implementation and expansion of the Program for the Prevention and Control of Infections and Antimicrobial Resistance (PPCIRA) (Figure 2) to all health units, but also on the implementation of the MRSA standard, the multimodal strategy for the Promotion of Basic Infection Control Precautions (PBCI) and the Antibiotic Prescription Support Program (PAPA) with reduction of quinolones/carbapenems.(71)

Regarding the most frequent resistant microorganisms currently, statistics from National Institute of Health Doctor Ricardo Jorge (INSA) indicate a decreasing trend since 2016, however some strains still have higher Portuguese averages than the European ones, namely the quinolone resistant *Escherichia coli* and *Acinetobacter baumannii* MDR with combined resistance to fluoroquinolones, aminoglycosides and carbapenems. There was also a large reduction in the mean levels of vancomycin-resistant *Enterococcus faecalis*, contrary to the exponential increase in carbapenem resistant *Klebsiella pneumoniae*, a common agent in urinary tract, respiratory and bloodstream infections whose proportion of patients isolated in 2016 increased by 73% compared to 2015, fact that was predictable given the increase of this strain in Europe.(71)

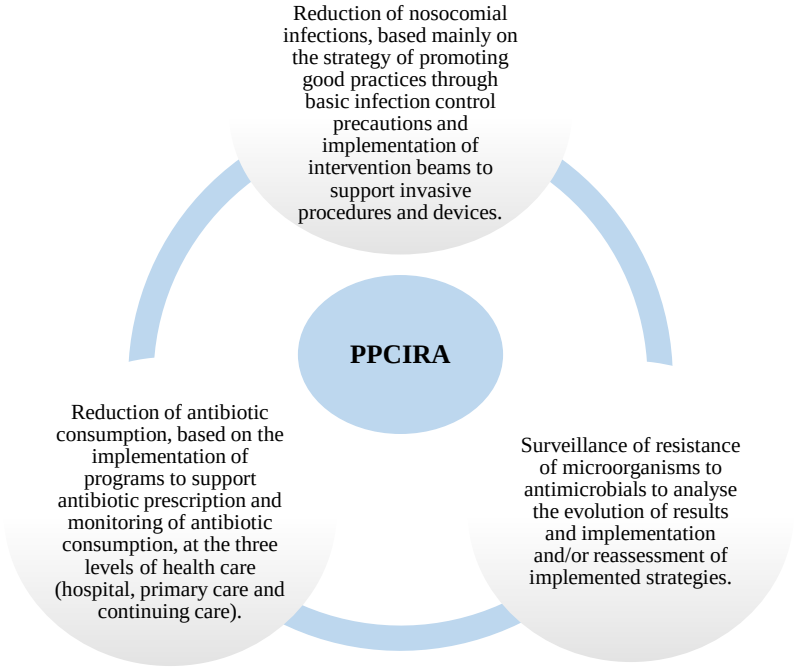

Figure 2. The three fundamental pillars of PPCIRA for the prevention and control of infections associated with healthcare and adverse drug reactions (52)

3 Conclusion

A healthy urinary tract is an open system bearing urine from renal tubules to urethra, having its own mechanisms of protection such as the natural microbiome (confirmed by sensitive diagnostic techniques and expanded quantitative urine cultures).

The main target of the treatment of ITUs is no longer the achievement of UT sterility, since without the beneficial microbiota, the UT may be thrown into a dysbiotic, sensitized state for colonization by uropathogens. There is evidence that both the infection itself and treatment strategies affect the urinary microbiome, constituting a disruptive mechanism of the defence barrier.

Typical uropathogens (such as UPEC) are rarely detected except in women experiencing UTI symptoms. Curiously, most of the standard urine culture protocols performed by clinical microbiology laboratories worldwide miss most of the non-*E. coli* uropathogens, arguing against the conventional *E. coli*-centric view of UTI.

The associated antibiotic overuse causes serious problems, not only for the specific patient safety but for the surrounding community. It is imperative to question the ease of antibiotics prescription, to promote their safe and effective use. The physician must question not only the state and type of infection, but if the current and most actualized evidence shows benefit in a certain patient's treatment.

To shift the paradigm of antibiotic resistance, new treatment strategies and prophylactic measures are emerging. The probiotics, which constitute a logical route for the development of novel therapies, the different prophylaxis vaccines that are being developed, and so on. Considering that the vaginal and microbial niches are predictably highly interconnected, vaginal microbiome transplantation may also be an option for the treatment of recurrent UTI. Thus, it is crucial to understand the relation between the healthy and unhealthy microbiota, for future improvement in prevention and treatment of the second most common disease in the community.

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