Treatment of acute prostatitis in family medicine practices at Split-Dalmatia Health Centre

Spaseska, Stela

UNIVERSITY OF SPLIT

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Stela Spaseska

TREATMENT OF ACUTE PROSTATITIS IN FAMILY MEDICINE PRACTICES AT SPLIT-DALMATIA HEALTH CENTRE

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Assoc. Prof. Marion Tomičić, MD, PhD

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LIST OF ABBREVIATIONS

GnRH – gonadotropin-releasing hormone
LH – luteinizing hormone
FSH – follicle-stimulating hormone
BPH – benign prostatic hyperplasia
UTI – urinary tract infection
DRE – digital rectal exam
PSA – prostate specific antigen
TURP – transurethral resection of the prostate
TRUS – trans-rectal ultrasound guided prostate biopsy
TNM staging system – tumor, node, metastasis staging system
ADT – androgen deprivation therapy
E. coli – Escherichia coli
STD – sexually transmitted disease
LPS – lipopolysaccharide
IL – interleukin
TNF-α – tumor necrosis factor alpha
PGE2 – prostaglandin E2
CBC – complete blood count
ISKRA – Intersectoral coordination mechanism for the control of antimicrobial resistance
mg – milligrams
AMR – antimicrobial resistance
WHO – World Health Organization
EU – European Union
EEA – European Economic Area
min – minimum
max – maximum
GP – general practitioner
NICE – National Institute for Health and Care Excellence

1. INTRODUCTION

1.1. Prostate anatomy and physiology

The prostate gland, an accessory gland of the male reproductive system, is situated in the lesser pelvis. Pyramidal in shape, its base is oriented upwards and its apex downwards. Located below the neck of the urinary bladder and above the urogenital diaphragm, the prostate is positioned behind the lower part of the pubic symphysis and anterior to the ampulla of the rec-tum. The base of the prostate is pierced by the urethra and ejaculatory ducts, while the apex is directed downwards towards the urogenital diaphragm, presenting four distinct surfaces. Anteriorly, the prostate is related to the retropubic space and is connected to the pubis by the puboprostatic ligaments. Posteriorly, it is adjacent to the lower third of the rectum. The gland receives its blood supply from the inferior vesical and middle rectal arteries, both branches of the anterior division of the internal iliac artery (1).

Structurally, the prostate contains three main components: the urethra, the ejaculatory ducts, and the prostatic utricle, a remnant of the Müllerian duct. According to traditional classification, the prostate is divided into five lobes: the anterior lobe, posterior lobe, median lobe, and two lateral lobes. The anterior lobe, located in front of the urethra, connects the two lateral lobes and is devoid of glandular tissue, hence referred to as the isthmus. The posterior lobe, situated behind the ejaculatory ducts, is commonly the origin of primary carcinoma. The median lobe is found behind the upper part of the urethra and in front of the ejaculatory ducts, while the lateral lobes lie on each side of the urethra (2). The prostate is enveloped by two capsules: a true capsule and a false capsule. It is classically described as being the size of a walnut, with glandular structures arranged into three zones: the transitional zone, the central zone, and the peripheral zone, the latter containing the highest concentration of glandular tis-sue and being the largest zone (3).

Prostate is innervated by both somatic and autonomic nerve fibers. Pudendal nerve (S2-S4), a major nerve in the pelvic region, having somatic nerve fibers, is responsible for sensory and motor function in the perineum (4). Autonomic nerve fibers consist of parasympathetic and sympathetic fibers. Pelvic splanchnic nerves (S2-S4) carry para-sympathetic fibers which take role in the relaxation of smooth muscle and facilitation of glandular secretion (5). Sympathetic fibers enter the hypogastric plexus, primarily from the lumbar splanchnic nerves (T10-L2) and have a role in controlling of ejaculation via inducing smooth muscle contraction (6).

There are several essential hormones in male reproductive physiology. Secretion of gonadotropin-releasing hormone (GnRH) from the hypothalamus acts on gonadotropic cells in the anterior pituitary gland to make and secrete luteinizing hormone (LH) and follicle-stimulating hormone (FSH). LH acts on Leydig cells located in the interstitium of the testes to

produce testosterone. Despite of its main functional role in development of male body characteristics, testosterone is essential for the primary stage of spermatogenesis, namely for growth and division of testicular germinal cells. FSH acts on Sertoli cells located in seminiferous tubules of the testes, where the process of spermatogenesis occurs, under the influence of these cells. Once the sperm is formed, it should be stored in the epididymis to develop its capacity of mobility. The sperm then moves through the vas deferens to reach the urethra. As it moves it mixes with the fluid secreted from both seminal vesicles and prostate as well as from the bulbourethral glands. Seminal vesicle fluid contains fructose, citric acid and large quantities of prostaglandins. Prostate secrete thin, milky, alkaline fluid, rich with essential nutrients for sperm protection and nourishment such as calcium, zinc, proteolytic enzymes, citrate ions and phosphate ions. The alkaline characteristic of the prostate fluid is crucial for successful fertilization since the female vaginal secretions are acidic, and the sperm can only survive in an alkaline environment (7).

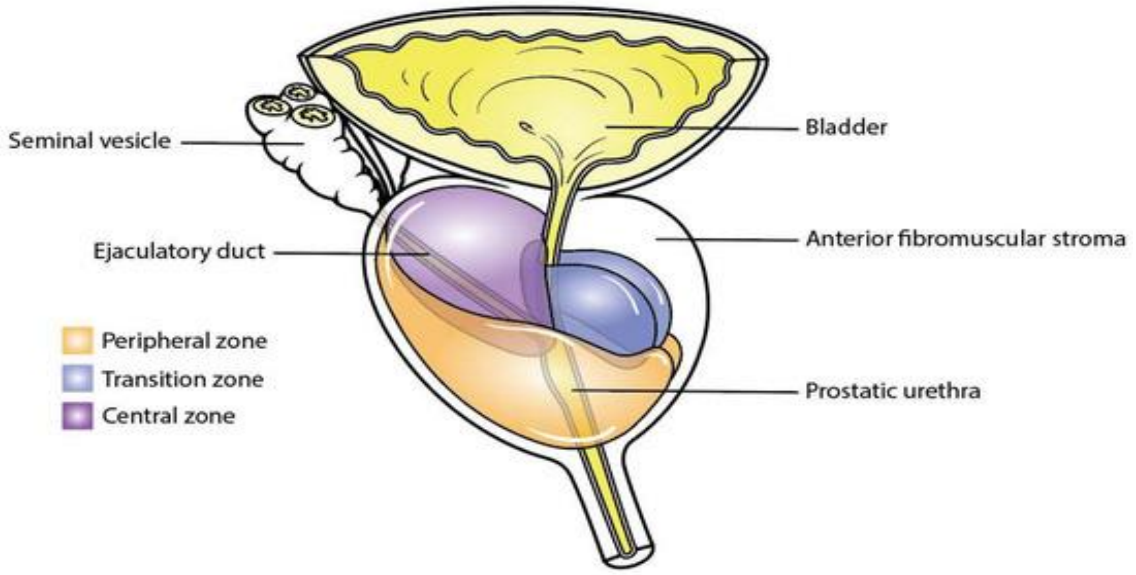

Figure 1. Three anatomical zones of the prostate gland. Source: Figiel S, Cancel-Tassin G, Mills IG, Lamb AD, Fromont G, Cussenot O. Molecular anatomy of prostate cancer and its implications in active surveillance and early intervention strategies. Anatomia. 2023;2:300-319.

1.2. Prostate gland disorders

There are three main prostate pathologies: prostatitis, benign prostatic hyperplasia (BPH) and prostate cancer (8).

1.2.1. Prostatitis

Prostatitis is the most common urological inflammation in males younger than 50 years and third most common urinary tract disease in men. Depending on clinical presentation and duration of the symptoms as well as microbiological isolates, National Institutes of Health has classified prostatitis in four different categories, such as: acute bacterial prostatitis, chronic bacterial prostatitis, chronic nonbacterial prostatitis or pelvic pain syndrome, and asymptomatic inflammatory prostatitis (9).

1.2.1.1. Classification of prostatitis

Acute bacterial prostatitis is bacterial infection of the prostate with sudden onset of symptoms such as severe pelvic pain, painful and frequent urination, urinary retention, and systemic symptoms like fever, nausea and chills (10).

Chronic bacterial prostatitis is persistent or recurrent bacterial infection of the prostate with duration longer than three months. In comparison to acute bacterial prostatitis, fever and chills are unusual symptoms. Besides dysuria and strong pelvic pain, ejaculatory pain is also present, causing sexual dysfunction and psychological issues. Common etiological factor is untreated or improperly treated urinary tract infection (UTI).

Chronic nonbacterial prostatitis or pelvic pain syndrome differs from chronic bacterial prostatitis by having sterile urine and undetectable bacteria, even though the symptoms and their duration are the same.

Asymptomatic inflammatory prostatitis does not cause any symptoms and it is incidentally found on physical or laboratory exam, proved by histopathological analysis (11).

1.2.2. Benign prostatic hyperplasia (BPH)

BPH is the most common urinary tract disease in men, mainly in older population. BPH is adenomatous enlargement of the prostate, affecting exclusively the transitional zone of the prostate. The urinary outflow obstructive symptoms are progressing as the prostate enlarges. Urgent, intermittent and frequent urination, especially at night, nocturia, is patient's main complaint. By digital rectal exam (DRE), smooth and firm enlargement can be detected. Laboratory analysis should be obtained such as measuring of prostate specific antigen (PSA).

Since PSA can be increased in other conditions like prostatitis and prostate carcinoma, more precise evaluation must be performed to exclude carcinoma of the prostate, including non-invasive ultrasound or prostate biopsy (12). There are pharmaceutical treatment options for BPH such as alpha-adrenergic antagonists, phosphodiesterase-5 inhibitors, and 5 – alpha reductase inhibitors, but in cases of more severe clinical presentation of the disease, transurethral resection of the prostate (TURP) is recommended (13).

1.2.3. Prostate cancer

Prostate cancer, most commonly adenocarcinoma affecting peripheral zones of the prostate, is second most common type of cancer in men over 65 and second most common urinary tract disease in men, after BPH. Palpation of hard and lumpy irregularity of the gland by DRE is the earliest and fastest way of raising suspicion of carcinoma. The gold standard for diagnosing prostate carcinoma is elevated PSA, together with transrectal ultrasound guided prostate biopsy (TRUS). Depending on the extent of the tumor, extend of spread to the lymph nodes and presence of metastasis (TNM) staging scale, there are different treatment options, starting from radical prostatectomy to androgen deprivation therapy (ADT) (14).

1.3. Acute bacterial prostatitis

Sudden onset of symptoms and sign of inflammation of the prostate gland typically caused by bacterial infection is called acute bacterial prostatitis.

1.3.1. Etiology

Acute bacterial prostatitis results in 10% of all cases of prostatitis. Most common causative organisms for acute prostatitis are gram-negative rods, by far the most frequent is the *Escherichia coli (E. coli),* accounting for most of the cases. Other possible genera of the family of *Enterobacteriaceae* except *Escherichia* are *Klebsiella*, *Proteus* and *Enterobacter*. Other potential bacteria such as *Pseudomonas*, sexually transmitted *Neisseria gonorrhoeae* and *Chlamydia trachomatis* and less commonly, exceptional gram-positive Enterococci can be involved (15). In most of the cases, the bacteria which live harmlessly in one ‘s body can occasionally leave their natural habitat, multiple and travel up to the urethra from where they spread to the prostatic ducts as ascending urethral infection. Another possible mechanism of bacterial spread is by pooling or blocking of the urine, in conditions such as enlarged prostate - BPH and renal stones. Less common contributing factors are procedures likes catheterization, cystoscopy and prostate biopsy. In younger population, sexually transmitted diseases (STDs)

are an important etiological factor. Although infrequent, hematogenous spread of bacteria to prostate for other body parts can also occur (16).

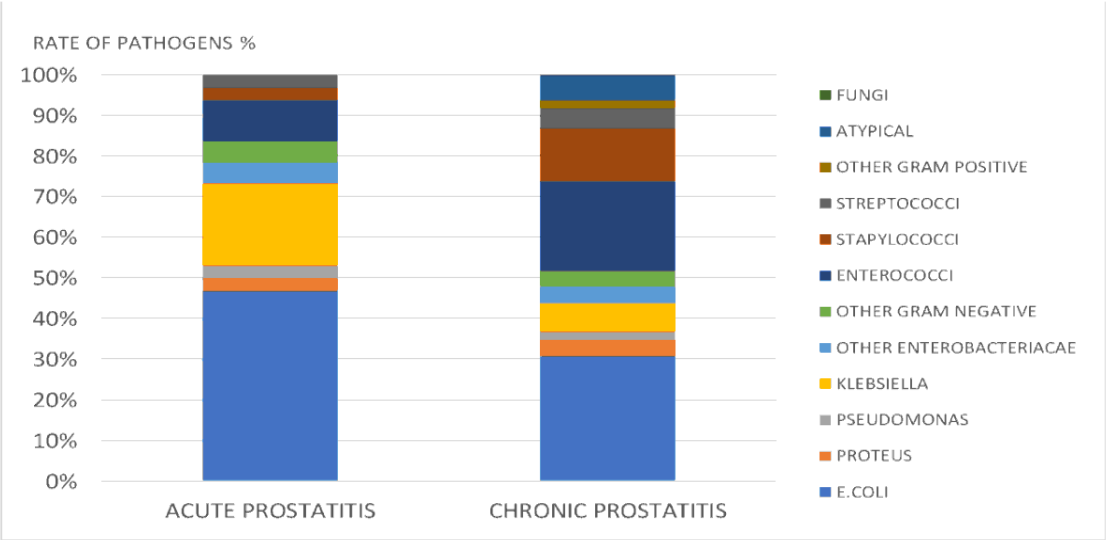

Figure 2. Isolated pathogens in both acute and chronic prostatitis. Source: Trinchieri A, Abdelrahman KM, Bhatti KH, Bello JO, Das K, Gatsev O et al. Spectrum of causative pathogens and resistance rates to antibacterial agents in bacterial prostatitis. Diagnostics. 2021;11:1333.

1.3.2. Epidemiology

According to Croatian health statistics yearbook 2022, subtotal number of patients with listed ICD-10 codes in family (general) medicine practices in Croatia in 2022 for the of the genitourinary system disorders N00-N99 was 809 264. Subtotal refers to the number of unique per-sons in the specified ICD-10 subgroup, hence each person is counted once, regardless of the number of diagnoses he/she has been attributed with.

N40-N51 refers to diseases of male genital organs. In this statistics yearbook N40 – Benign prostate hyperplasia was divided as separate entity, while diseases ranging from N41-N51 were analyzed together as other diseases of male genital organs. Total number of patients with N41-N51 was 63 062, out of which exact number of N41 Inflammatory diseases of prostate or more precisely N41.0 Acute prostatitis is not known. They have divided the patients by age group from 0-6, 7-19, 20-64 and 65 + with number of patients diagnosed 1.114, 4.906, 37.043, 19.999 and 63.062 respectively (17).

1.3.3. Pathogenesis of acute prostatitis

The pathogenesis of prostatitis, particularly acute bacterial prostatitis, involves a complex interplay of infectious agents, bacterial virulence factors and host anatomical and immune factors. Bacterial ability to cause an infection is determined by its virulence factors. These factors play important role in bacterial colonization, immune invasion, nutrient acquisition and host damage.

1.3.3.1. Bacterial virulence factors

The most important virulence factors of the gram-negative rods that contribute to prostatitis are adhesins, toxins, enzymes, antigenic structures, biofilm formation and siderophores. Adherence factors or adhesins facilitate attachment of the bacteria to the tissue surface via their long, thick rod like appendages (*pilus*, *pili*) and short hair-like structures (*fimbria*, *fimbriae*) special surface molecules. Toxins are divided in two categories: exotoxins, proteins produced inside of both gram positive and gram-negative bacteria and endotoxins or lipopolysaccharide (LPS) which are part of the outer membrane exclusively made by gram negative bacteria. These toxins cause direct damage of the host tissue and disruption of normal cellular processes. Bacterial secretion systems are cell membrane protein complexes which are essential for interaction between bacteria and host's eukaryotic cells. One of the functions of these secretion systems is to secrete tissue degrading enzymes, further contributing to infectious process (18). *Enterobacteriaceae* family has several antigenic structures that are key to their pathogenicity and are also used for serotyping, a crucial way of grouping and distinguishing different strains of microorganisms. The primary antigenic structures include the O antigen, H anti-gen, and K antigen. O antigen is a core polysaccharide, part of the LPS layer located on the outer membrane of the bacteria. It contributes to the structural integrity of the bacteria and plays a crucial role in the immune response by acting as an endotoxin. H antigen is associated with the bacterial flagella. It is a protein called flagellin that forms the filament of the flagella. It is responsible for chemotaxis, bacterial motility toward favorable environments. K antigen is a type of specific polysaccharide located on the bacterial capsule. It is involved in virulence and immune evasion, together with the capsule which provides protection against phagocytosis by the host immune cells (19). Aggregation of bacteria to each other in an exopolysaccharide matrix is call biofilm. The role of the biofilm is to protect the bacteria from the host's immune mechanisms as well as to make a diffusion barrier for antimicrobials. In this way the treatment is difficult since antibiotic resistance is increased compared to similar bacteria living in a planktonic state. The last but not the least is the requirement for iron. Since iron is an essential

nutrient not only for the humans, but also for the microorganisms, some of these bacteria have ability to efficiently obtain and accumulate iron for their growth and metabolism via synthesizing and secreting low molecular weight iron-chelating molecules called siderophores (20).

1.3.3.2.Host immune response

Immune response is the ability of the immune system to defend against pathogens, eventually eradicating the infection. There are two types of immunity: innate and adaptive. Innate or non-specific immunity is the first line, immediate response to a pathogen. Prostate epithelium not only serves as a protective physiologic barrier but also has short acting capacity to provide the immediate defense against infection (21). Inflammatory response to bacterial invasion of the prostate starts by recognition the bacteria via pattern recognition receptors such as Toll-like receptors. This leads to further chemotaxis of phagocytic leukocytes such as polymorphonuclear leukocytes (neutrophils) and mononuclear phagocytes (monocytes), which differentiate into macrophages once entering extravascular tissues. They recognize, ingest and destroy of the engulfed organism via process of phagocytosis. These cells also release cytokines including interleukin-1 (IL-1) and tumor necrosis factor alpha (TNF-α) and other mediators such as prostaglandins and leukotrienes that elicit further inflammatory changes.

Five cardinal signs of inflammation are *rubor* (redness), *calor* (warmth/heat), *tumor* (swelling), *dolor* (pain), and *functio laesa* (loss of function). The inflammatory mediators are responsible redness and warmth via dilation of the local blood vessels. Hyperemia or increased blood flow to the prostate cause some plasma leakage out of the blood vessels causing tissue swelling, so called edema. As the edema progresses, it presses against pain receptors and nerve endings causing pain and eventually loss of function (22).

Adaptive or specific immunity is slower and more specialized defense against infection. It is divided into cell mediated (cellular) via T lymphocytes and antibody mediated (humoral) immunity via B lymphocytes. The protective role of adaptive immunity in prostatitis is unclear. However, both cellular and humoral-mediated immunity may contribute to tissue damage via continuous immune response and tissue remodeling if not regulated properly.

One of the possible complications is chronic prostatitis which results in chronic inflammation due to inadequate resolution of the infection either by improper immune response or improper treatment. Another possible complication due to persistent or severe infection are abscess formation and rarely, life threatening systemic spread from the infected prostate, leading to bacteremia and sepsis (15).

1.3.3.3. Fever development

Substance that can rise the hypothalamic set point temperature are called pyrogens. Both exogenous and endogenous pyrogens contribute to fever development. Bacterial endotoxins of the gram-negative bacteria, so called exogenous pyrogens, stimulate the host's immune cells to produce and release endogenous pyrogens or pro-inflammatory cytokines IL-1, IL-6 and TNF-α. IL-1 is by far most important endogenous pyrogen. It directly influences the hypothalamus to produce fever as well as indirectly via production of prostaglandin E2 (PGE2), which acts on the hypothalamic thermoregulatory center to elicit the fever reaction (23).

1.3.4. Signs and symptoms of acute prostatitis

Infectious and inflammatory processes due to both bacterial virulence factors and host immune response manifest as signs and symptoms of acute bacterial prostatitis. Both constitutional symptoms such as pain, fever, chills, arthralgia, myalgia, and malaise, as well as urinary tract symptoms, dysuria, urinary frequency, urgency and urinary retention can be present. Compression of the urethra and irritation of the bladder due to the prostatic inflammatory edema obstruct the urine flow leading to symptoms such as urinary frequency, urgency and urinary retention. Inflammation of the prostate additionally causes spasms of the pelvic floor muscles and affects the surrounding pelvic nerves, which results in abnormal sensations, discomfort, and pelvic pain. Bacterial infection directly irritates the urethra and bladder, contributing to dysuria or painful urination. Rapid onset high grade fever in acute bacterial prostatitis accompanied by other constitutional symptoms, reflect the body's widespread inflammatory response (24).

1.3.5. Diagnosis

Diagnosis of acute bacterial prostatitis is based on detailed medical history, presenting symptoms, clinical findings on physical exam, and laboratory tests. After taking medical history, the physician should perform DRE. On DRE lobes, sulcus, size, consistency, mobility of the prostate as well as accessible lymph nodes if present should be palpated. In patients with acute prostatitis, the prostate is soft, warm and painful on palpation. Anal sphincter can be hypertonic. If there is a sensation of fluctuation, a prostate abscess should be suspected as potential complication of prostatitis. Release of prostatic expressate may be stimulated by prostate massage. In acute prostatitis the prostatic fluid shows presence of leukocytes, but this method is contraindicated since it may result in bacteremia and sepsis. Useful diagnostic tests

for acute prostatitis are urinalysis, as well as semen culture, complete blood count (CBC), together with prostate specific antigen (PSA) levels measurement. Leukocytosis is shown on CBC. PSA values up to 4 ng/ml are considered normal. Even though PSA is elevated in acute prostatitis, it should be noted that PSA is organ specific, but not disease specific. In case of unclear diagnosis, family medicine physicians should send their patients to urology specialist for further diagnostic analysis such as transrectal ultrasound examination (24). Proper urine collection is essential for correct urinalysis results. The procedure must be explained to the patient. First-voided morning, midstream urine should be collected in sterile container. The procedure includes retraction of the foreskin and cleansing of the meatus. First part of the stream should not be collected, but the midstream portion. Urine color, odor, clarity and specific gravity along with chemical urine test strips (dipsticks) which measure urine pH, protein, glucose, hemoglobin levels as well as number of nitrite (bacteria) and leukocyte esterase activity (leukocytes) are part of macroscopic urine examination. It is fast and practical method to exclude genitourinary infection, especially when nitrite and leukocyte esterase are negative. Positive nitrite test suggests the presence of >100,000 organisms per milliliter, pointing to significant bacteriuria and leukocyte esterase indicates the presence of white blood cells. Hematuria or blood in urine can occasionally be present in acute prostatitis. It can be visible to the naked eye, macrohematuria or visible only under the microscope, microhematuria. When there are any positive findings on macroscopic urinalysis, a microscopic urinary sediment examination should be performed. The positive microscopic findings should be confirmed by bacterial culture. It is an important method for estimating the number of bacteria, for identifying both organisms involved and suitable drug for treatment. Urine specimen that contains 105 or more bacteria per milliliter indicates a bacterial infection, but a lower count does not rule out the possibility of an infection, especially in a symptomatic patient. Urine culture most frequently identifies *E. coli* in acute prostatitis. Since *E. coli* is sensitive to numerous antibiotics, it is not common practice to determinate its antibiotic sensitivity. However, in patients with comorbidities such as renal insufficiency or diabetes mellitus or in patients with uncommon bacterial infections, it might be necessary to identify the antibiotic sensitivity (25).

1.4. Treatment recommendations

Recommendations for antibiotic treatment of prostatitis are similar around the world. There are some factors which have influence on choosing and prescribing the most suitable drug. By far most important factor in Croatian health system when prescribing certain drug is

the referral to tertiary healthcare for specialists' approval. For instance, urologist must recommend and approve treatment of acute bacterial prostatitis with fluoroquinolones (26).

1.4.1. ISKRA Guidelines

Intersectoral Coordination Mechanism for the Control of Antimicrobial Resistance (ISKRA) guidelines for prostatitis were created in Croatia, based on the former guidelines published until 2010, the newer international guidelines published in the period from 2011 to 2014 and the Croatian scientific research project "Research into the etiology, epidemiology, diagnosis and treatment of patients with the prostatitis syndrome", which took place in the period from 2010 to 2013, following the principles of Appraisal of Guidelines for Research and Evaluation (AGREE) methodology for guidelines' quality. These guidelines cover the classification, diagnosis, and treatment of prostatitis. They aim to standardize and optimize the diagnostic and therapeutic processes, as well as to ensure the rational use of antibiotics. General practitioners (GPs) and specialists in both primary healthcare and hospital settings are considered to be following these guidelines when prescribing antimicrobial therapy for prostatitis (26).

1.4.1.1. **Treatment of acute prostatitis according to ISKRA guideline**

Symptoms of acute bacterial prostatitis can differ from mild to severe. When the symptoms are mild, hospitalization is not required, and the patients can be treated in family medicine practice by their physician. Considering that the most common pathogens in acute prostatitis are gram-negative rods, the first therapy of choice are antibiotics with good oral bioactivity, favorable pharmacokinetics, an excellent penetration into the prostate, and good safety profile like fluoroquinolones. The first line of choice is oral therapy with fluoroquinolones of wider spectrum, such as 2nd generation ciprofloxacin or 3rd generation levofloxacin, 500 milligrams (mg) daily, lasting from ten days to four weeks. In some cases, a treatment duration of six weeks is recommended to avoid recurrence of infection three months after starting therapy. Fluoroquinolones, like other drugs, can lead to adverse effects, the most prevalent of which are skin rashes and gastrointestinal distress like nausea, vomiting and diarrhea. However, it is crucial to recognize that more severe adverse effects, such as phototoxicity, tendinitis, tendon rupture, central nervous system effects like headaches, dizziness, confusion, and insomnia, are infrequent. On the other hand, when the general condition of the patient with acute bacterial infection is severe, they must be hospitalized and treated with parenteral antimicrobial therapy lasting for seven to ten days. Broad-spectrum

penicillins, 3rd generation cephalosporins or fluoroquinolones, possibly all combined with aminoglycosides, are part of empirical antibiotic parenteral therapy (as written in Table 1). Beta-lactam antibiotics are not recommended of primary use. The antimicrobial therapy should be corrected according to the antimicrobial susceptibility test, antibiogram. In case of resistance due to bacterial biofilm formation or drug hypersensitivity reaction, second line antimicrobial treatment should be initiated with parental administration of carbapenems for seven to ten days or two to three weeks of oral or parental administration of combination of trimethoprim-sulfamethoxazole, co-trimoxazole. An adequate hydration, analgesics, antipyretics and alpha-blockers should be given in combination with antibiotics to relieve the symptoms. After improvement of patient's general condition, they should continue with oral fluoroquinolones therapy for two to four weeks. Surgical treatments should be avoided during acute infection, expect in complications such as urine retention, when suprapubic puncture or suprapubic catheter should be placed to drain the urine from the bladder or when it is necessary to drain the prostate abscess (26).

Table 1: Drugs used in the treatment of acute prostatitis

First line antimicrobial treatment	**Second line antimicrobials in case of resistance and/or hypersensitivity**	**Drugs used in combination with antimicrobials**
3rdgeneration Cephalosporins +/- Aminoglycosides	Carbapenems	Alpha-blockers
Aminopenicillins + beta-lactamase inhibitors	Co-trimoxazole	Non-steroidal anti-inflammatory drugs
Fluoroquinolones		Steroidal anti-inflammatory drugs

Source: Kraus O, Bukovski S, Mađarić V, Škerk V, Štimac G, Vukelić D et al. HDKM [Internet]. Zagreb HR: Zavod za urogenitalne infekcije, Klinika za infektivne bolesti "Dr. Fran Mihaljević"; 2023 [updated 2023; cited 2024 June 25]. Available from: https://www.hdkm.hr/wp-content/uploads/2017/02/ISKRA-smjernice-prostatitis.pdf

In younger population, *Chlamydia trachomatis*, *Ureaplasma urealyticum*, *Mycoplasma genitalium* and *Mycoplasma hominis* are important causative agents of prostatitis. Both patient and their sexual partner must get treated for STDs. Treatment options include azithromycin, a

macrolide antibiotic, 500 mg daily, for three weeks administered only on first three days of the week, with or without 500 mg of levofloxacin, a fluoroquinolone antibiotic, every day, for two to four weeks. In case of resistance or intolerance, second choice of treatment includes twice a day of 100 mg doxycycline, a tetracycline antibiotic, for three to four weeks (26).

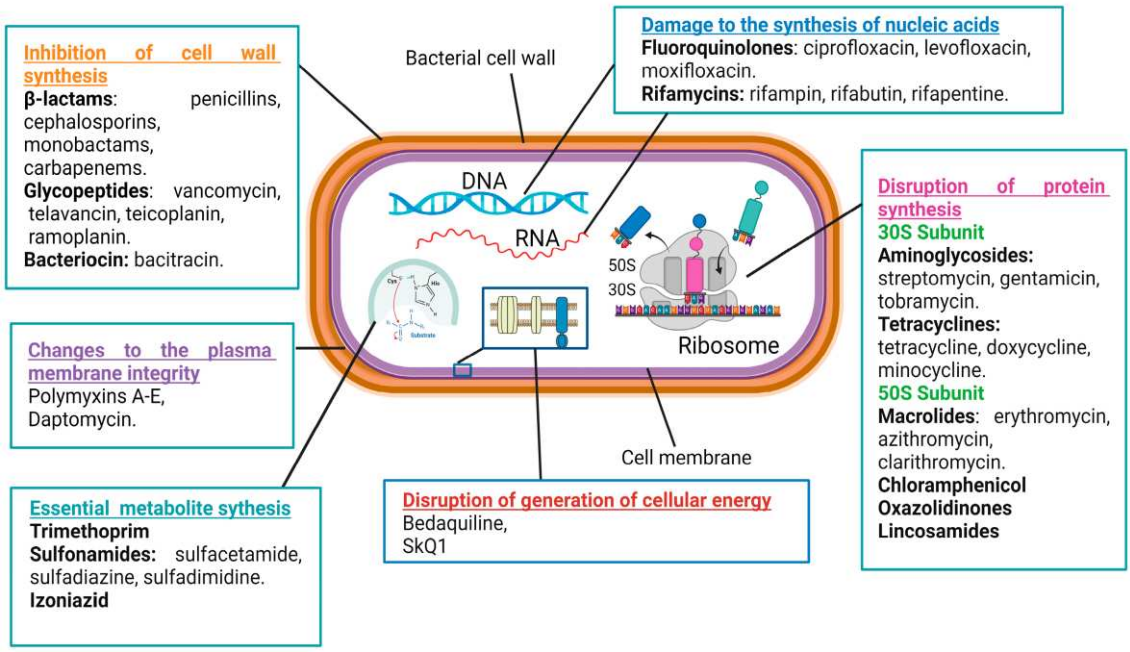

Figure 3. Six different mechanisms of action of antibiotics. Source: Eshboev F, Mamadalieva N, Nazarov PA, Hussain H, Katanaev V, Egamberdieva D et al. Antimicrobial action mechanisms of natural compounds isolated from endophytic microorganisms. Antibiotics. 2024;13:271.

1.4.2. The importance of rational drug prescribing

Rational drug prescribing is a critical component of healthcare, aimed to ensure that patients receive the most appropriate medications for their clinical needs. This involves deep understanding of pharmacology, in order to select the right drug, at the right dose, for the right duration of treatment. Effective prescribing requires a thorough understanding of the patient's medical history, current health status, and any other medications they may be taking, since co-administration may cause drug interaction. The goal of rational prescribing is to maximize therapeutic benefits while minimizing the risks of adverse effects and drug resistance development via avoiding unnecessary medications and reducing polypharmacy. To achieve this, physicians must rely on clinical guidelines and evidence-based practices to make informed

decisions. They must stay updated with the latest medical research and drug information to ensure they are choosing the best drug for a single individual. Additionally, clear and open communication with patients is essential for explaining the purpose of the medication, how to take it properly, and discussing potential side effects. Selecting generic medications at a lower cost, which can provide the same therapeutic benefits as brand-name drugs is another important consideration in rational prescribing (27).

1.4.3. The danger of antimicrobial resistance

Drugs used for treatment of infectious diseases are called antimicrobials. Depending on the type of the microorganism they are used for, antimicrobials can be divided into antibiotics, antivirals, antifungals and antiparasitics. When antimicrobials are overused or inappropriately prescribed, they can become lose their potency and become ineffective or resistant. Antimicrobial resistance (AMR) represents a big challenge in medicine, even in the treatment of bacterial prostatitis. World health organization (WHO) surveillance data from Europe, the European Union (EU), and the European Economic Area (EEA) indicate a growing trend of antibiotic resistance in *E. coli*, the most common causative agent of prostatitis. In 2020, Fluoroquinolones resistance rates in E. coli was higher in southern and eastern parts of Europe, accounting from 25% to 50% of AMR rates, while it was lower in northern and western parts of Europe. Nor-way was the only European country with the lowest AMR rate of 8%, while North Macedonia was observed to have more than 50% of AMR rates. On the other hand, the resistance to third-generation cephalosporins in *E. coli* varied significantly across the European countries, ranging from 5% to 10% in some countries, to more than 50% of AMR rates in other countries. Carbapenem-resistant *E. coli* used to be low, but the rising rates of more than 1% in some non-EU/EEA European countries is highly concerning. In 2020, EU/EEA countries have reported 46% or 45 338 fully susceptible *E. coli* isolates to antibiotics, out of total 138 793 isolates. More than half or 54% of the *E. coli* isolates were resistant to one (33%) or more (21%) antibiotics. Even though, EU/EEA countries reported an annual decrease in AMR rates from 2016 to 2020, there were still 54.6% AMR rates for aminopenicillins, followed 23.8% for fluoroquinolones, 14.9% for third-generation cephalosporins and 10.9% for amino-glycosides. Lower AMR rates, 0.2%, for carbapenems were observed, compared to the statistical analysis which included non-EU/EEA European countries as well (28).

According to Croatian Academy of Medical Sciences, in the period from 2000 to 2021, there was a significant increase in *E. coli* resistance to antibiotics in Croatia (as shown in the figure 4).

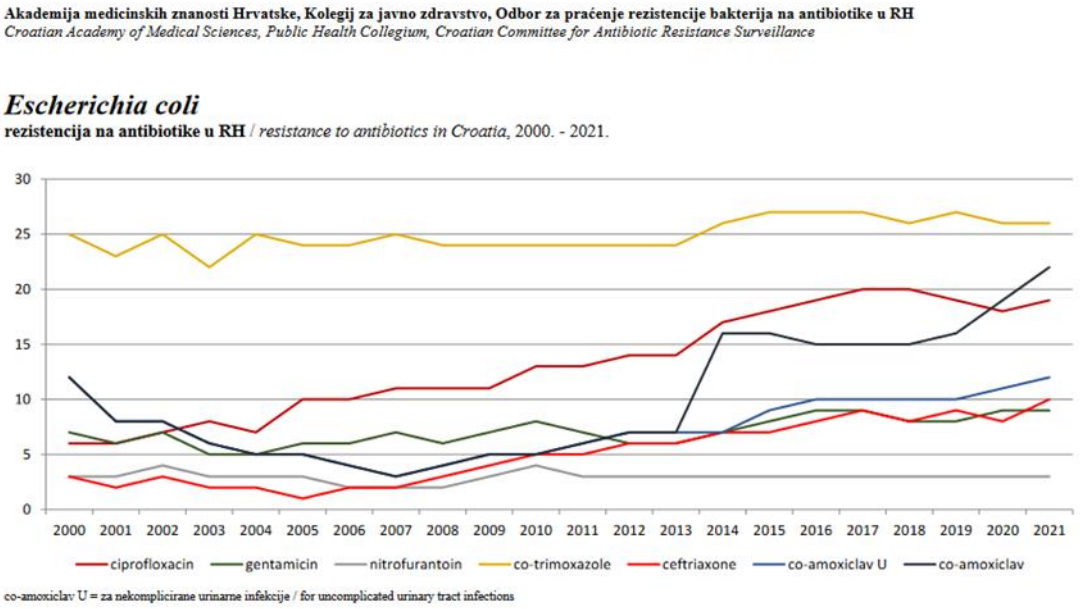

Figure 4. *E. coli* resistance to antibiotics in Croatia throughout the years. Source: Andrašević A, Žmak Lj, Obrovac M, Payerl Pal M, Bukovski S, Hunjak B et al. Osjetljivost i rezistencija bakterija na antibiotike u Republici Hrvatskoj u 2021.g [Internet]. Zagreb HR: The Croatian Academy of Medical Sciences; 2021 [updated 2021; cited 2024 July 14]. Available from https://iskra.bfm.hr/wp-content/uploads/2022/11/Knjiga-2021-za-web-final.pdf

The data collected for *E. Coli* resistance from 39 centers in Croatia in the period of 01.10 – 31.12.2023 showed the following results: 48% out of 18 825 isolates were resistant to ampicillin, while the resistance rate was only 12% out of 18 717 isolates when amoxicillin was combined with clavulanic acid. Resistance to co-trimoxazole was observed in 26% out of 18 809 isolates. Highest resistance rate, 11%, of all cephalosporins was seen to cefixime in 18 482 isolates, while no resistance was recorded to ceftazidime/avibactam in 16 483 isolates. AMR rates was 19% for both ciprofloxacin and norfloxacin in 18 444 and 18 732 isolates respectively (29).

Although not a common practice, identifying the causative bacteria and determining their antibiotic susceptibilities would lead to rational treatment of prostatitis via selecting the most effective antibiotic, thereby reducing the likelihood of prolonged illness, recurrent infections, or progression to chronic infection due to the resistance development. Misuse of antibiotics, including improper dosing, incomplete courses of treatment, use the leftover medications for self-diagnosed future illnesses or for non-bacterial infections, accelerates the emergence of resistant strains. Educating both healthcare providers and patients about proper

antimicrobial use and the danger of AMR is essential for successful future treatment of any infectious disease (30).

2. OBJECTIVES

2.1. Main research objective

The main objective of this research was to determine whether family medicine doctors follow the recent ISKRA guidelines when prescribing antibiotics for the treatment of acute prostatitis.

2.2. Secondary research objective

Secondary objective was to determine whether family medicine doctors refer the patients with acute prostatitis to urologist for their treatment.

2.3. Research hypotheses

1. Family medicine doctors fully follow the recommendations of the ISKRA guidelines when choosing antibiotics for the treatment of acute prostatitis.

2. Family medicine doctors refer the patients with acute prostatitis to urologist for their treatment.

3. MATERIALS AND METHODS

In eight family medicine practices of Split-Dalmatia Health Centre, a retrospective, cross-sectional study was conducted on the frequency and treatment methods of acute prostatitis in the period from January 1, 2023, to June 15, 2024.

3.1. Permission from the Ethics Committee

The study was approved by the Ethics committee of the Split-Dalmatia Health Centre, based on the Article 41 of the statute of Split-Dalmatia Heath Centre, class: 007-04/24-02/007; registration number: 2181-149-19-24-002.

3.2. Basic information about the family medicine doctors

Before starting the research, a request was sent to selected family medicine doctors employed in Split-Dalmatia Health Centre. The research was presented to the doctors with an emphasis on the objectives, protection of the patient's identity and methods of data collection. All doc-tors (8) who were requested, accepted and allowed collection of the required data. The data was collected in the period from 17.06.2024 until 01.07.2024 in their practices. For the research, data were taken from the electronic record of the insured patients under the care of the respondent, that is, those who were examined in the specified period and were diagnosed ac-cording to the International Classification of Diseases 10 (ICD 10) of acute prostatitis (N41).

3.3. Basic patient information

The collected data for each patient included sex, age, present symptoms, physical exam, laboratory analysis such as PSA measurement and urine analysis, diagnosis according to the International Classification of Diseases 10 (ICD 10) of acute prostatitis (N41) and treatment, including the group of the antibiotic, dose and duration of the following. Only males were included in the research. Exclusion criteria were incorrectly entered diagnoses, failure to pre-scribe antibiotics and female gender.

3.4. Statistical processing

Patients` data were obtained by adapting the software solution Softmed 2, Vegasoft d.d. (Rijeka, Croatia), and were extrapolated from the medical records in the family medicine practices in the form of an Excel table. All statistical analyses were performed in GraphPad Prism version 9.0.0 (GraphPad software, San Diego, USA). The normality of data distribution was determined by the Shapiro-Wilk test. Correlations between age, PSA levels, and duration of antibiotic treatment were measured by Spearman’s correlation coefficient. The significance

of differences in age, PSA levels, and duration of antibiotic treatment between groups was tested using the Mann-Whitney U test. The significance of association between categorical variables was determined with the Chi-square test. Statistical significance was set at $P < 0.05$.

4. RESULTS

A retrospective, cross-sectional study on the frequency and treatment methods of acute prostatitis was conducted in eight family medicine practices located in Split, Croatia, in the period from January 1, 2023 to June 15, 2024. The average number of patients per one practice was 1693 (minimum (min.) 1248, maximum (max.) 2110). Only males were included in this re-search study. The collected data for each patient diagnosed with N41 included age, present symptoms, physical exam, PSA measurement urine analysis, and treatment, including the group of the antibiotic, dose and duration of the following. Total number of patients diagnosed with N41 was 121. Number of incorrectly diagnosed patient was 21 and those were excluded from the study. 100 out of 121 patients entered in the inclusion criteria. 89 out of 100 patients had acute prostatitis, while the rest 11 had relapse of chronic prostatitis. The youngest patient was 19, while the oldest was 89. Most commonly prescribed antibiotics were fluoroquinolones, counting for 64 out of 100 patients, among which ciprofloxacin was most commonly prescribed (38), followed by levofloxacin (19), norfloxacin (6) and moxifloxacin (1). Second most commonly prescribed drug was amoxicillin + clavulanic acid, which belongs to the group of aminopenicillins + beta-lactamase inhibitors. Only 2 patients were treated with 3rd generation cephalosporins, such as cefixime. Others were treated with azithromycin, a macrolide antibiotic, cefuroxime, 2nd generation cephalosporin, nitrofurantoin, a nitrofuran antibiotic, doxycycline, a tetracycline antibiotic and cephalexin, 1st generation cephalosporin (as shown in Figure 5.).

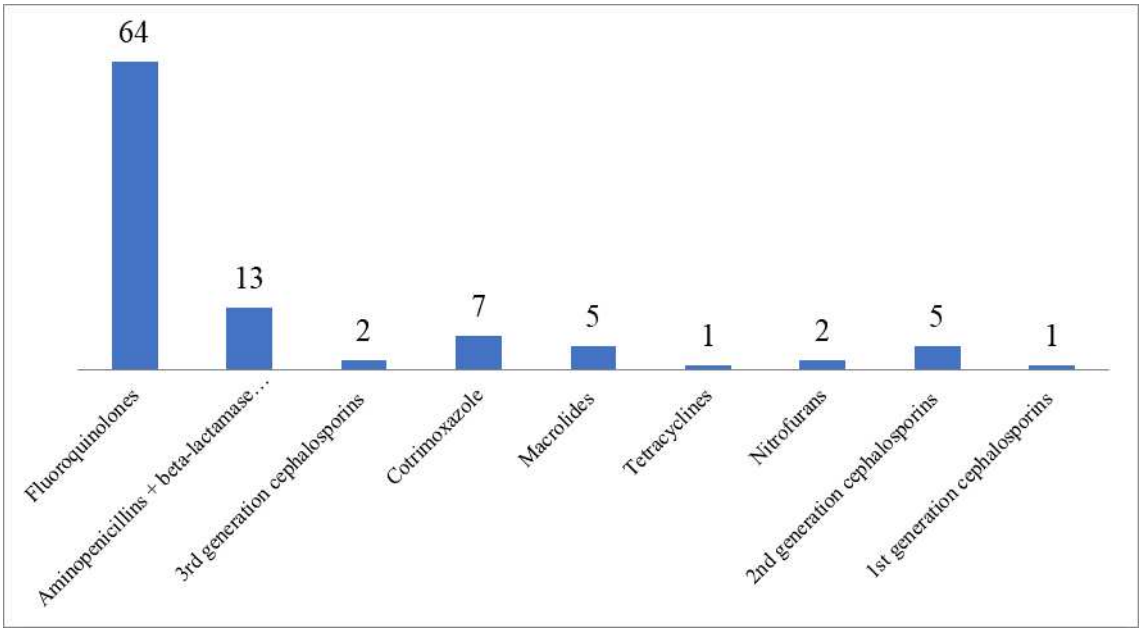

Figure 5. Antibiotics used in treatment of acute prostatitis

4.1. Age

There was a significant positive correlation between patients' age and PSA levels (r = 0.553, $P < 0.001$), as well as between the age and duration of antibiotic treatment (r = 0.256, $P = 0.017$). There was a statistically significant difference in the age of patients regarding their referral to a urologist ($P < 0.001$), with the patients referred to a urologist being significantly older compared to those not referred. The patients whose GP prescribed first-line treatment according to the ISKRA guidelines were also significantly older compared to those whose first-line treatment did not follow the guidelines ($P = 0.014$). There was no statistically significant difference in the patients' age regarding the chronicity of the prostatitis, presence of symptoms, who performed the DRE, results of urine analysis, or whether originally prescribed treatment was changed (Table 2).

Table 2. Correlation between age and categorical variables

Category	Age, years	*P* value
Prostatitis		
acute (N = 89)	63 (50 – 74)	0.281
chronic (N = 11)	72 (53 – 83)	
Symptoms		
present (N = 89)	63 (50 – 74)	0.418
not present (N = 11)	71 (53 – 74)	
DRE performed by		
general practitioner (N = 44)	60 (42.25 – 73.5)	0.088
another specialist (N = 56)	66.5 (53.5 – 74)	
Referred to urologist		
yes (N = 76)	67 (58 – 74.75)	< 0.001
no (N = 24)	51.5 (33.25 – 62.5)	
Urine analysis findings		
normal (N = 61)	63 (50 – 73)	0.446
abnormal (N = 29)	68 (53 – 75.5)	
ISKRA guidelines for		
treatment	65 (53 – 74)	0.014
followed (N = 79)	57 (33.5 – 68.5)	
not followed (N = 21)		
Original treatment switched		
yes (N = 13)	72 (61 – 77.5)	0.091
no (N = 87)	63 (48 – 73)	

Data are presented as median (interquartile range). *P*-values were calculated using the Mann-Whitney U test.

4.2. PSA levels

There was a significant positive correlation between PSA levels and duration of antibiotic treatment (r = 0.36, $P < 0.001$). There was a statistically significant difference in the PSA levels of patients and the one who performed the physical exam, including DRE ($P < 0.013$), with the patients examined by another specialist rather than their GP having significantly higher results than those who were firstly examined by their GP. There was also a

statistically significant difference in the PSA levels of patients regarding their referral to a urologist ($P < 0.001$), with the patients referred to a urologist having significantly higher PSA values compared to those not referred. The patients whose GP prescribed first-line treatment according to the ISKRA guidelines also had significantly higher PSA values compared to those whose first-line treatment did not follow the guidelines ($P = 0.020$). The patients whose original treatment was changed had significantly higher PSA values compared to those whose therapy remained the same ($P = 0.016$). There was no statistically significant difference in the patients' PSA levels regarding the chronicity of the prostatitis, presence of symptoms or results of urine analysis. (Table 3).

Table 3. Correlation between PSA levels and categorical variables

Category	PSA, ng/mL	*P*-value
Prostatitis		
acute (N = 89)	2.38 (1.19 – 5.66)	0.214
chronic (N = 11)	4.40 (1.38 – 8.76)	
Symptoms		
present (N = 89)	2.29 (1.16 – 5.44)	0.058
not present (N = 11)	5.36 (1.88 – 7.55)	
DRE performed by		
general practitioner (N = 44)	1.52 (1.04 – 5.94)	0.013
another specialist (N = 56)	3.62 (1.82 – 6.24)	
Referred to urologist		
yes (N = 76)	3.4 (1.59 – 7.55)	< 0.001
no (N = 24)	1.28 (0.91 – 2.14)	
Urine analysis findings		
normal (N = 61)	2.53 (1.16 – 5.42)	0.311
abnormal (N = 29)	2.42 (1.36 – 9.10)	
ISKRA guidelines for treatment		
followed (N = 79)	3.10 (1.21 – 6.64)	0.020
not followed (N = 21)	1.38 (1.04 – 2.19)	
Original treatment switched		
yes (N = 13)	6.42 (2.00 – 16.64)	0.016
no (N = 87)	2.33 (1.16 – 5.32)	

Data are presented as median (interquartile range). *P*-values were calculated using the Mann-Whitney U test.

4.3. Duration of treatment

There was a statistically significant difference in the duration of patients' treatment and the one who performed the physical exam, including DRE ($P < 0.024$), with the patients examined by another specialist rather than their GP having significantly longer duration of treatment compared to those who were firstly examined by their GP. There was also a statistically significant difference in the duration of treatment and patients' referral to a urologist ($P < 0.001$), with the patients referred to a urologist having significantly longer

duration of treatment compared to those not referred. The patients whose GP prescribed first-line treatment according to the ISKRA guidelines also had significantly longer treatment duration compared to those whose first-line treatment did not follow the guidelines ($P < 0.001$). There was no statistically significant difference in the patients' PSA levels regarding the chronicity of the prostatitis, presence of symptoms, results of urine analysis or whether originally prescribed treatment was changed (Table 4).

Table 4. Correlation between duration of treatment and categorical variables

Category	Duration of treatment, days	*P*-value
Prostatitis		
acute (N = 86)	15 (10 – 24.25)	0.792
chronic (N = 7)	10 (10 – 28)	
Symptoms		
present (N = 87)	15 (10 – 24)	0.953
not present (N = 6)	15 (8.75 – 28.5)	
DRE performed by		
general practitioner (N = 40)	10 (7 – 21)	0.024
another specialist (N = 53)	20 (10 – 28)	
Referred to urologist		
yes (N = 70)	20 (10 – 28)	< 0.001
no (N = 23)	10 (7 – 14)	
Urine analysis findings		
normal (N = 54)	12 (10 – 21)	0.101
abnormal (N = 29)	20 (10 – 28)	
ISKRA guidelines for treatment		
followed (N = 73)	20 (10 – 28)	< 0.001
not followed (N = 20)	10 (5.5 – 18.25)	
Original treatment switched		
yes (N = 13)	21 (10 – 28)	0.141
no (N = 80)	14 (10 – 21)	

Data are presented as median (interquartile range). *P*-values were calculated using the Mann-Whitney U test.

4.4. Associations

The relation between the chronicity of prostatitis and the presence of symptoms was significant ($P < 0.001$). Patients with acute prostatitis were more likely than those with chronic prostatitis to present with symptoms. There was no significant association between the chronicity of prostatitis or the presence of symptoms with any of the other categorical variables analyzed (Table 5.)

Table 5. Association between chronicity of prostatitis and the presence of symptoms

	Acute prostatitis	**Chronic prostatitis**	**Total**
Symptoms present	83	6	89
Symptoms absent	6	5	11
Total	89	11	100

There was a significant association between whether a DRE was performed by the GP and the patient being referred to a urologist, ($P = 0.002$). Patients whose GP performed a DRE were less likely to be referred to a urologist than those whose GP did not perform the DRE. Another significant association was found between whether a DRE was performed by the GP and ISKRA guidelines for first-line treatment being followed, ($P < 0.001$). Patients whose GP performed a DRE were less likely to be given first-line treatment according to ISKRA guidelines than those whose GP did not perform the DRE. Additionally, there was a significant association between whether a DRE was performed by the GP and if the initially prescribed treatment was switched to another, ($P = 0.002$). Patients whose GP performed a DRE were more likely to have their initially prescribed treatment changed than those whose GP did not perform the DRE (Table 6.).

Table 6. Associations between DRE and urologist referral, ISKRA guidelines and initial therapy switch

	DRE performed by GP	**DRE performed by another specialist**	**Total**
Patient referred to urologist	27	49	76
Patient not referred to urologist	17	7	24
Total	44	56	100
ISKRA guidelines followed	27	52	79
ISKRA guidelines not followed	17	4	21
Total	44	56	100
Initial therapy switched	11	2	13
Initial therapy not switched	33	54	87
Total	44	56	100

There was a significant association between whether a patient was referred to a urologist and ISKRA guidelines for first-line treatment being followed, ($P < 0.001$). Patients who were referred to a urologist were more likely to be prescribed initial treatment according to ISKRA guidelines than patients who were not referred to a urologist (Table 7.).

Table 7. Urologist referral and ISKRA guidelines recommendations association

	Patient referred to a urologist	**Patient not referred to a urologist**	**Total**
ISKRA guidelines followed	69	10	79
ISKRA guidelines not followed	7	14	21
Total	76	24	100

There was a significant association between the results of urine analysis and whether initially prescribed treatment was switched to another, (P = 0.038). Patients whose urine analysis findings were abnormal were more likely to have their initially prescribed treatment changed than those whose urine analysis findings were normal (Table 8.).

Table 8. Urine analysis results and initial therapy switch association

	Urine analysis findings normal	**Urine analysis findings abnormal**	**Total**
Initial therapy switched	5	7	12
Initial therapy not switched	56	22	78
Total	61	29	90

5. DISCUSSION

The main objective of this study was to find out if family medicine doctors/GPs in Croatia follow the ISKRA guidelines in treatment of acute prostatitis, while the secondary objective was to observe if they refer their patients to a urologist for the treatment. The study was conducted in eight family medicine practices in Split. There were 121 patients diagnosed with prostatitis in the period of 01.01.2023 to 15.06.2024 and but 100 were included in the data, since 21 were misdiagnosed. Patients' data were collected and results were interpreted. Data included patients' age, present symptoms, physical exam together with DRE, diagnostic methods including PSA values and urine analysis, urologist referral and drug used for treatment plus duration of the treatment.

According to the ISKRA guidelines the first-line drugs for treatment of acute prostatitis are 3rd generation cephalosporins ± aminoglycosides, aminopenicillins + beta-lactamase inhibitors, ureidopenicillins + beta-lactamase inhibitors and fluoroquinolones. Second-line antimicrobials should be considered only in case of hypersensitivity reaction or drug resistance, they include carbapenems and co-trimoxazole. Macrolides or tetracyclines, in case of resistance or intolerance to macrolides, can be used in younger population if STDs are proven to be the cause of illness (26). 79 out of 100 patients were treated with the first-line options. Most commonly prescribed drugs were fluoroquinolones, counting for 64 out of 100 patients, among which ciprofloxacin was most commonly prescribed, followed by levofloxacin, norfloxacin and moxifloxacin. Second most commonly prescribed drug was amoxicillin + clavulanic acid (13 out of 100), which belongs to the group of aminopenicillins + beta-lactamase inhibitors. Only 2 patients were treated with 3rd generation cephalosporins. ISKRA guidelines were not followed for 21 patients. 7 out of 21 were treated with co-trimoxazole, second-line drug of treatment, without any previous record of resistance or intolerance of the first-line drugs. Others were treated with azithromycin, a macrolide antibiotic, medications from the 2nd generation cephalosporins, nitrofurantoin, a nitrofuran antibiotic, doxycycline, a tetracycline antibiotic and medications from the 1st generation cephalosporins. On the other hand, The National Institute for Health and Care Excellence (NICE) guidelines for the treatment of acute prostatitis, published in October 2018, states that the first-line of treatment should be ciprofloxacin or ofloxacin. It is interesting to note that they consider trimethoprim as an alternative first-line treatment, while trimethoprim/sulfamethoxazole (co-trimoxazole) is part of the second-line choice and can be only prescribed after specialists' approval. Levofloxacin is also considered as second-line choice according to NICE guidelines (31).

The aim of this ISKRA guideline is to improve the quality of care for the patient, by choosing the most appropriate drug and to achieve rational drug prescribing, by establishing

the goals of the therapy (26). Rational prescribing is the key factor for reducing the inappropriate use of antimicrobials and slowing down the development or progression of antimicrobial resistance. AMR became a big problem not only in Croatia, but globally, in the last two decades due to the misuse of the antimicrobials, especially antibiotics. Asking for antibiotics' prescription even for non-bacterial infections, non-completion of the treatment once feeling better or self-diagnosing and using the leftovers from the former treatment, are some of the most common patients' mistakes which led to increasing of AMR these twenty years (27). Comparing the results from Croatian Academy of Medical Science and from the National Clinical Care Database, we can conclude that they both proved that there was a significant increase in resistance to fluoroquinolones, due to their overuse in the treatment of prostatitis, especially in cases of non-infectious prostatitis. It is essential to educate not only the patients, but also the physicians about the importance of proving the cause of the disease as well as about the rational prescription and use of the medications in order to prevent bigger issues with AMR in the near future (29, 32).

One important factor when prescribing certain medications in Croatian health system is the referral to tertiary healthcare for specialists' approval. In this study, 76 out of 100 patients were referred to urologist and 69 of them were treated according to ISKRA guidelines, which is a significant association. On the other hand, patients who were not referred to a urologist, were less likely to be prescribed initial treatment according to ISKRA guidelines. This is in accordance with the fact that, in Croatia, in order for family medicine doctors to prescribe fluoroquinolones, urologists must first recommend and approve the treatment (26). We compared this with North Macedonian health system, since both of these countries used to have the same health system 30 years ago. We found out that North Macedonia follow Evidence-based medicine (EMB) guidelines for treatment of acute prostatitis. The first-line treatment are oral fluoroquinolones, most commonly ciprofloxacin and norfloxacin or trimethoprim-sulfamethoxazole. In cases of worsening of the clinical picture, the patient should be hospitalized and treated with intravenous cefuroxime. In contrast to Croatian health system, the family medicine doctors/GPs in North Macedonia do not need to refer their patients to a urologist for the fluoroquinolones treatment approval (33).

Patients with prostatitis most commonly present with sudden onset of symptoms such as severe pelvic pain, painful and frequent urination, urinary retention, and systemic symptoms like fever, nausea and chills (10). We found a significant relation between the chronicity of prostatitis and the presence of symptoms, 83 out of 89 patients had symptomatic acute prostatitis, while only 6 out 11 who had relapse of their chronic prostatitis had symptoms. This

was in line with a previous study which determined that, in comparison to acute prostatitis, patients with chronic prostatitis experience less or no symptoms (11).

In this study, 44 patients had a DRE performed by their GP, while 56 were examined by another specialist. Considering that a diagnosis of acute prostatitis is confirmed by both presenting symptoms and the clinical findings on physical exam, including DRE, PSA values and urinalysis (23), the patients whose GP performed a DRE were less likely to be referred to a urologist since all examinations to make a diagnosis of prostatitis were done in the family medicine practice. These patients were also less likely to follow the first-line treatment ISKRA recommendation guidelines since, as mentioned before, they were not referred to a urologist.

There was also a significant association between the results of urine analysis and whether initially prescribed treatment was switched to another. 61 out of 100 patients had normal urinalysis findings, 29 had bacterial infection and 10 were not sent for urinalysis. Out of those 90 patients, the therapy was changed to 12 of them. Patients whose urine analysis findings were abnormal were more likely to have their initially prescribed treatment changed than those whose urine analysis findings were normal. We compared our results with another study which as well showed that initial antibiotic treatment was adjusted according to the urine culture and sensitivity outcomes from urine tests and that later treatment usually involved fluoroquinolones (34).

We found a significant positive correlation between the patients' age and PSA levels, as well as between the age and duration of antibiotic treatment, also between PSA levels and duration of antibiotic treatment. These correlations have been explored in several studies. One of them shows that serum PSA levels increase even in older healthy men. Prostate volume is one the several factors in this correlation, since the prostate increases in the process of aging, which causes variation in the PSA values (35). Another study showed that when patient is older, the duration of the treatment would be prolonged, ranging from 4 up to 12 weeks. As people age, they have increased likelihood of comorbid conditions, their immune system becomes weaker and their clinical presentation is usually more severe. In order to eradicate the infection completely and to prevent further complications it is necessary to prolong the treatment (36).

The cross-sectional studies are designed to observe data at one specific point in time, which can lead to temporal bias. Since acute prostatitis is an episodic condition, the short time frame of this study could not have captured all seasonal or annual variations of this disease. The data was collected retrospectively from patients' medical records, which led to informational bias due to occasional incomplete patient's documentation. Excluding the misdiagnosed patients highlights the potential issues with diagnostic accuracy in the medical records. Other

limitations of this study were the small sample size and the limited number of family medicine practices. It is essential to recall that most common drugs prescribed for acute prostatitis are fluoroquinolones, which require urological approval. Single-city focus of this study led to geographical bias, since the treatment of the disease might have differed in other areas of this region, especially because urban population has better access to tertiary healthcare, compared to population from the islands and other rural areas. Despite the disadvantages of this study, we proved the hypotheses that family medicine doctors/GPs follow the ISKRA guidelines in treatment of acute prostatitis as well as that they refer their patients to a urologist for the treatment.

6. CONCLUSION

1. Family medicine doctors fully follow the recommendations of the ISKRA guidelines when choosing antibiotics for the treatment of acute prostatitis.
2. Family medicine doctors refer the patients with acute prostatitis to urologist for their treatment.

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8. ENGLISH SUMMARY

Objectives: The main objective of this research study was to determine which antibiotics were prescribed by family medicine doctors for the treatment of acute prostatitis and to compare the results with the recent ISKRA guidelines. The secondary objective was to determine whether the patients with acute prostatitis were referred to urologist for their treatment.

Materials and methods: This study was conducted in eight family medicine practices of Split-Dalmatia Health Centre. Patients' data were obtained from their medical records by adapting the software solution Softmed 2, Vegasoft d.d. Each patient diagnosed with N41, inflammatory diseases of the prostate and treated with antibiotics in the period of 01.01.2023 to 15.06.2024 was included in the study.

Results: There was a statistically significant difference in following ISKRA guidelines for treatment of acute prostatitis as well as referring the patients to urologist in correlation with age of the patient, PSA levels and the duration of the treatment.

Conclusion: Family medicine doctors follow the recommendations of the ISKRA guidelines when choosing antibiotics for the treatment of acute prostatitis and they refer the patients with acute prostatitis to urologist for their treatment.

9. CROATIAN SUMMARY

Naslov: Liječenje akutnog prostatitisa u ordinacijama obiteljske medicine Doma zdravlja Splitsko-dalmatinske županije.

Ciljevi: Glavni cilj ovog istraživanja bio je utvrditi koje su antibiotike propisivali liječnici obiteljske medicine za liječenje akutnog prostatitisa i usporediti rezultate s nedavnim ISKRA smjernicama. Sekundarni cilj bio je utvrditi jesu li pacijenti s akutnim prostatitisom upućivani urologu na liječenje.

Materijali i metode: Ovo istraživanje provedeno je u osam ordinacija obiteljske medicine Doma zdravlja Splitsko-dalmatinske županije. Podaci o pacijenatima dobiveni su iz njihovih medicinskih kartona prilagodbom softverskog rješenja Softmed 2, Vegasoft d.d. U istraživanje su uključeni svi pacijenti kojima je dijagnosticirana šifra N41, upalne bolesti prostate, i koji su liječeni antibioticima u razdoblju od 01.01.2023 do 15.06.2024.

Rezultati: Postojala je statistički značajna razlika u pridržavanju ISKRA smjernica za liječenje akutnog prostatitisa, kao i u upućivanju pacijenata urologu, u korelaciji s dobi pacijenta, razinom PSA i trajanjem liječenja.

Zaključci: Liječnici obiteljske medicine pridržavaju se preporuka ISKRA smjernica pri odabiru antibiotika za liječenje akutnog prostatitisa te upućuju pacijente s akutnim prostati-tisom urologu na liječenje.