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A MODERN APPROACH TO THE PROBLEM OF TREATING UREAPLASMA INFECTION

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Annotation: The article presents the main characteristics of ureaplasmas, discusses methods of diagnosis, treatment and prevention of ureaplasma infection. It is noted that it is necessary to identify both specific and non-specific pathogens in a timely manner in order to prescribe optimal antibacterial therapy. Special attention is paid to the macrolide antibiotic josamycin, which is recommended by leading urologists as a first–line drug for the treatment of ureaplasma and mycoplasma infections and, if prescribed in a timely manner, can achieve a complete cure in 97.5% of cases. In recent decades, the frequency of ureaplasma and mycoplasma infections has increased significantly, which most often affects the genitourinary system in women. However, experts still doubt whether ureaplasmosis can be considered a separate disease, since its causative agent is found in the vagina in healthy women in 60%, and in newborn girls in 30% of cases [1, 2].

Key words: ureaplasma, sensitivity to antibiotics josamycin, adhesins, urease, PCR.

Purpose: the article presents the main features of Ureaplasma, discusses methods for diagnosing, treating and preventing ureaplasma infection. In order to prescribe Optimal antibacterial therapy, the need for timely detection of pathogens that do not contain os and self-sos has been noted. Particular attention is paid to the antibiotic of the macrolide group – josamycin.

Materials and methods: 51 patients were selected who were admitted to the scientific center of Urology of the Republic. Patients are divided into 2 groups. 34 were placed in the control group and 17 in the main group.

Results: Special attention is paid to josamycin, a macrolide antibiotic that is recommended by leading urologists as a first - line drug in the treatment of Ureaplasma and mycoplasma infections and, when prescribed on time, allows full treatment in 97.5% of cases. Reduces to 5.9%.

Conclusion: thus, the choice of an antibiotic for ureaplasma infection should be based on the results of microbiological studies on the outflow of the female genital organs. Improving diagnostic tests for the detection of specific and non-specific pathogens allows you to achieve the maximum results of antibacterial therapy in this category of patients. Timely use of vilpraphen allows ureaplasmosis to be treated in 97.5% of cases. The high clinical efficacy of vilpraphen makes this antibiotic very important for the treatment of sexually transmitted diseases.

- The first representatives of the Mollicutes class were described in 1896 by E. Nocard and E. Roux as the causative agent of atypical pleuropneumonia in cattle, but detailed research of these microorganisms began only since the early 1960s, when the first artificial culture media for

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mycoplasma cultivation were proposed. Until that time, it was generally assumed that mycoplasmas are the L-forms of bacteria. This did not allow them to be considered as an independent taxonomic unit in the classification of microorganisms. The introduction of the DNA hybridization method into microbiological practice in the early 1970s made it possible to prove that mycoplasmas are an independent group called the Mollicutes class [3, 4].

- The Mollicutes class are prokaryotes without a cell wall that are unable to synthesize a–E-diaminopimelic acid, as a result of which they are osmotically unstable and exhibit plasticity and a variety of forms. Representatives of the Mollicutes class (mycoplasmas, acholeoplasmas, spiroplasmas, ureaplasmas, and anaeroplasmas) are characterized by a number of features unique to prokaryotes: extremely simple cell organization with a minimal number of organelles; lack of cell wall; the lowest G+C ratio (guanine + cytosine) base pairs in their DNA, the smallest genome size among prokaryotes (0.5–1.0 MDa).

On a solid nutrient medium, these microorganisms form colonies with a dense center growing into agar and a lighter periphery, the size of the colonies varies from 50 to 500 microns. The surface part of the colony is usually made up of larger cells, while the central, deeper part is made up of smaller, optically denser cells [2, 5]. The reproduction of mycoplasmas occurs through the usual cell division, the breakdown of filaments into coccoid cells, while the process of division of mycoplasmas generally does not differ from that of other bacteria. Being facultative parasites, mycoplasmas depend on the host for a wide range of nutrients, therefore they grow in a complex environment in which the role of most components is difficult to determine. Mollicutes use their ability to hydrolyze arginine and process glucose as an energy source. The latter process is based on the type of glycolysis, and its result is the production of lactic acid. Ureaplasma spp. hydrolyzes urea to form ammonia and carbon dioxide. For growth and reproduction, all Mollicutes require multicomponent media containing sterols, nucleic acid precursors, at least 12 amino acids, and B vitamins [3, 4]. Ureaplasmas, as representatives of mycoplasmas, belong to the kingdom of Procariotae, department Tenericutes, the Mollicutes class, they are included in the order Mycoplasmatales, a family of Mycoplasmataceae and are grouped into the genus Ureaplasma. This genus includes U. urealyticum and U. diversum. At the same time, the human parasite is U. urealyticum, and U. diversum is detected in cattle and other animals [2, 6]. Ureaplasma urealyticum was first isolated by M. Shepard in 1954. from a patient with non-gonococcal urethritis. The peculiarity of the biology of ureaplasmas is also expressed in their relatively rapid growth. The growth curve of ureaplasmas coincides with that of mycoplasmas in the latent phase and the early logarithmic phase, but the stationary phase is reached in 16-18 hours. The optimum pH of the growth medium for ureaplasmas is lower than for most mycoplasmas, and is 6.0–6.5. In a dense medium, ureaplasmas are better cultivated in an atmosphere of a gas mixture consisting of 95% N2 and 5% CO2 or 5% O2, 10% CO2 and 85% N2. According to electron microscopic observations, U. urealyticum cells can be divided into 3 types: small (120-150 nm) – with homogeneous cytoplasm and multiple ribosomes; medium (500-750 nm) – with ribosomes on the periphery; large ones – with an optically denser inhomogeneous cytoplasm and a pronounced nucleoid. Ureaplasmas do not reduce tetrazole and do not have catalase activity. They differ from other Mollicutes in their ability to synthesize both saturated and unsaturated fatty acids. Ureaplasmas produce the pigment hypoxanthine, a product of purine metabolism, and have soluble beta–hemolysin, which is active against rabbit and guinea pig red blood cells.With the help of specific antisera, it was possible to isolate 14 U serotypes. urealyticum. These serotypes can be combined into two biovars – Parvo and T-960.

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The Parvo biovar includes serotypes 1, 3, 6 and 14; to the biovar T-960 – 2, 4, 5, 7-13 [1, 4]. Currently, the role of biovars in the development of pathological manifestations of ureaplasma infection is being intensively investigated. It is assumed that the Parvo biovar is more pathogenic than the T-960 biovar.Currently, it is believed that the pathogenic properties of ureaplasmas are manifested in certain conditions of the body, which are characterized by a decrease in resistance to pathogenic agents and are determined by their ability to attach to the epithelium of mucous membranes, the formation of endo- and exotoxins and other toxic chemical compounds. Pathogenicity factors for U. urealyticum are:

1. Adhesives are the surface components of cells whose function is to bind the cells of a microorganism to the target cells of a macroorganism. They play a crucial role in the development of the initial stage of the process. The adhesion of mycoplasmas to target cells occurs in 2 stages: 1st is the stage of non–specific interaction; 2nd is the stage of ligand-receptor interaction (the function of the ligand is performed by adhesin, the function of the receptor is performed by the corresponding structures of the membrane of the target cell of a glycoprotein nature). Adhesives may have antigenic properties and be species- and serotype-specific. Information has been obtained on the adhesion of ureaplasmas to human epithelial cells, erythrocytes, and spermatozoa. Recent studies show the presence of several adhesins in ureaplasmas. 2. Human IgA protease. It was found that the proteases of U. urealyticum cleaves human IgA into 2 fragments, corresponding in mass to Fc and Fab fragments. As a result of exposure to proteases, immunoglobulins lose their ability to bind ureaplasmic antigens and prevent the development of infecti

3. Phospholipases. Phospholipases A1, A2, and C were found in the ureaplasmic membrane, and the activity of phospholipase A2 was 60 to 300 times higher than that of phospholipase A1. It is assumed that these phospholipases, upon infection of the fetus and placenta, hydrolyze the phospholipids of the cell membrane of the placenta, which leads to an increase in the amount of free arachidonic acid and activation of prostaglandin synthesis.4. Urease. As noted above, U. urealyticum has urease activity. The hydrolysis of urea produces ammonia, which has a toxic effect on target cells.Ureaplasma infection is characterized by long-term persistence. U. urealyticum can cause acute infection, however, latent forms of infection are observed in most cases. Specific therapy helps to stop the clinical signs, but the elimination of the pathogen often does not occur, while the acute form of infection becomes latent. Persistent ureaplasmas can be activated under the influence of various factors (infection of another etiology, changes in the immune status of the body). Risk factors for infection with U. urealyticum are young age, low socio-economic status, early onset of sexual activity, large number of sexual partners, use of oral contraceptives, pregnancy [5]. Statistically reliable data on the prevalence of U. There are very few urealyticums in different countries of the world among different population groups, however, it is known that the frequency of colonization of the genitourinary organs by ureaplasmas in women is significantly higher (up to 60%) than in men. Individual studies suggest the presence of U. urealyticum in clinically healthy individuals. Ureaplasmas have been part of the indigenous (obligate) vaginal microflora since childhood. It has been proven that the colonization frequency depends on a woman's sexual activity. In adolescence, the frequency of detection increases from 8-10% in girls with a history of no sexual intercourse to 23-55.4% after the onset of sexual activity.Among gynecological patients, U. urealyticum is detected in 49-55% of cases, this may be due to the presence of clinical symptoms in women and more frequent screening [7, 8].

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Ureaplasma infection can be accompanied by inflammatory processes of the genitals, leading to infertility, termination of pregnancy, premature birth, prenatal fetal pathology, as well as cause urethritis, prostatitis and infertility in men [5]. Ureaplasmosis is one of those infections that a woman should be screened for before an expected pregnancy. Even a small number of microorganisms in the genitourinary tract of a healthy woman during pregnancy can become active and lead to the development of ureaplasma infection. At the same time, newly discovered ureaplasmosis during pregnancy is not an indication for termination of pregnancy, since ureaplasma does not have a teratogenic effect. However, ureaplasmosis can cause various complications during pregnancy. According to the literature, the incidence of neonatal neonatal neonatal infection ranges from 5.3 to 32.6%. Newborns, more often premature infants, develop acute pneumonia, chronic lung diseases with bronchopulmonary dysplasia, inflammatory diseases of the upper respiratory tract, conjunctivitis, meningitis, sepsis [4]. It should be emphasized that ureaplasmas rarely exist as a monoinfection. The most frequent associations are with facultative anaerobic microorganisms, somewhat less often with chlamydia, and even more rarely with viruses. U. urealyticum is most often (73-79%) found in association with Gardnerella vaginalis, less often with Chlamydia trachomatis (25-30%), M. hominis (21.4%) and other pathogens. The frequent (up to 75-80% of cases) detection of ureaplasmas simultaneously with anaerobic microflora may be due to the ability of G. vaginalis secretes succinic acid, which is used by other opportunistic microorganisms. In turn, ureaplasmas, which actively use oxygen for their vital activity, contribute to the increased reproduction of anaerobic bacteria [1, 4]. The frequent association of ureaplasmas with other microorganisms makes it difficult to resolve the question of their role as the main etiological factor or concomitant agent that enhances the pathological process. The fact of sexual transmission of ureaplasma infection is beyond doubt. In addition, a vertical transmission mechanism is possible, which in some cases can lead to the development of intrauterine fetal infection and infection by household contact.It is believed that the incubation period of ureaplasmosis lasts about one month. However, it all depends on the initial state of health of the infected person. Ureaplasma, once in the genital tract or in the urethra, may not manifest itself for many years. The resistance of the genitals to the effects of microorganisms is provided by physiological barriers, while the main factor of protection is the normal microflora. When the ratio of different microorganisms is disrupted, ureaplasma begins to multiply rapidly.According to the duration of the disease, there is a distinction between fresh urogenital ureaplasmosis (with a duration of infection of up to 2 months), which can be acute, subacute, sluggish, and chronic (with a duration of infection of more than 2 months), which is characterized by a low-symptom course. Given the frequent asymptomatic carriage of this infection, from a practical point of view it is quite difficult to determine the prescription of infection. The diagnosis of fresh urogenital ureaplasmosis is most reliable in the case when the pathogen was not detected during the examination of discharge from the genital tract during the last 2 months, and after the onset of clinical manifestations it began to be diagnosed. In addition, this diagnosis may also be valid if symptoms of the inflammatory process appear after the onset of sexual activity (change of sexual partner, sexual violence, etc.) in combination with the detection of the pathogen in diagnostically significant titers [1, 3]. Diagnosis of ureaplasma infection is based on laboratory examination data, taking into account the medical history and clinical symptoms.When analyzing anamnestic data, the patient's age, the presence of sexually transmitted diseases, the age of the onset of sexual activity, the number of sexual partners and the method of contraception used are taken into account. At the same time, the gynecological history is often burdened by the presence of infertility and inflammatory diseases of the

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genitourinary system, the obstetric history is characterized by unfavorable pregnancy outcomes, as well as a high incidence of infectious complications.It should be noted that ureaplasmosis is manifested by minor symptoms that do not bother patients much, and in most cases the disease does not manifest itself at all. Patients complain of clear vaginal discharge that appears from time to time, not much different from normal. Some women may experience a burning sensation when urinating. If there is a significant decrease in immunity, then ureaplasma can move higher up the genital tract, causing endometritis or salpingoophoritis.

Research methods. A combination of several methods was used for reliable laboratory diagnosis of ureaplasmosis [1, 3, 10]: 1. Polymerase chain reaction (PCR). It was a very fast method, and it took 5 hours to complete. If PCR shows the presence of ureaplasma in the patient's body, it means that it makes sense to continue the diagnosis. A negative PCR result of almost 100% means that there is no ureaplasma in the human body. However, PCR does not allow quantifying the characteristics of the pathogen, so a positive result in PCR is not an indication for treatment, and the method itself cannot be used for monitoring immediately after treatment.2. Bacteriological (cultural) diagnostic method. The material from the vagina, cervix, and urethra is placed on a nutrient medium, where ureaplasmas are grown for several days (usually 48 hours). This is the only method that allows you to determine the number of ureaplasmas, which is very important for choosing further tactics. Thus, with a titer of less than 104 CFU/ml, the patient is considered a carrier of ureaplasmas and most often does not require treatment. A titer of more than 104 CFU/ml requires drug therapy. The same method is used to determine the sensitivity of ureaplasmas to certain antibiotics before prescribing them, which is necessary for the proper selection of antibacterial therapy. Such a study usually takes about 1 week.3. Serological method (detection of antibodies). Detection of antibodies to ureaplasma antigens is used to determine the causes of infertility, miscarriage, and inflammatory diseases in the postpartum period. 4. Direct immunofluorescence (PIF) and immunofluorescence analysis (ELISA). They are quite widespread due to their relatively low cost and ease of execution, but their accuracy is low (about 50-70%). Indications for the treatment of infections caused by Ureaplasma spp. are: clinical and laboratory signs of inflammation of the genitourinary system; Upcoming invasive procedures in the area of the genitourinary system; Burdened obstetric and gynecological history; The complicated course of a real pregnancy. Treatment of ureaplasmosis is usually performed on an outpatient basis. Since the causative agent of this disease adapts very easily to various antibiotics, sometimes even several courses of treatment do not bring results. Microbiological examination of ureaplasma with determination of sensitivity to antibiotics can help in choosing a drug. In non-pregnant women, tetracycline drugs (tetracycline, doxycycline), fluoroquinolones (ofloxacin, pefloxacin) and macrolides (azithromycin, josamycin, clarithromycin) are used. During pregnancy, only some of the macrolides can be used, and tetracycline-type drugs and fluoroquinolones are contraindicated [3]. Recently, data have appeared in the literature on a decrease in the sensitivity of genital mycoplasmas to fluoroquinolones and tetracyclines, and therefore their use is not recommended. The effectiveness of local therapy and immunotherapy is currently not proven [3].The most widely used antibiotic for the treatment of urogenital ureaplasmosis is currently josamycin (Vilprafen®). Vilprafen® is recommended by leading urologists as a first-line drug for the treatment of ureaplasma and mycoplasma infections. In in vitro studies, josamycin demonstrates the highest activity against ureaplasmas in comparison with other macrolides. In addition, it should be noted that josamycin (Vilprafen®) is the only approved drug for use during pregnancy

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[4].Vilprafen® is an antibiotic of the macrolide group, the mechanism of action of which is associated with a violation of protein synthesis in a microbial cell due to reversible binding to the 50S subunit of the ribosome. In therapeutic concentrations, it usually has a bacteriostatic effect, slowing down the growth and reproduction of bacteria, and when high concentrations are created in the focus of inflammation, it has a bactericidal effect.Unlike many other antibiotics, Vilprafen® penetrates well into cells and creates high intracellular concentrations, which is important in the treatment of infections caused by intracellular pathogens. It is also important that this antibiotic is able to penetrate phagocytic cells such as macrophages, fibroblasts, and polymorphonuclear granulocytes and transport them to the inflammatory focus [5]. After ingestion of Vilprafen® It is rapidly absorbed from the gastrointestinal tract, with the maximum concentration reached 1-2 hours after ingestion. 45 minutes after taking a 1 g dose, the average plasma concentration of josamycin is 2.41 mg/l. Binding to plasma proteins does not exceed 15%. Taking the drug with an interval of 12 hours ensures that the effective concentration of josamycin in the tissues is maintained throughout the day. The equilibrium state is reached after 2-4 days of regular intake. In addition, it penetrates well through biological membranes and accumulates in various tissues: in the lung, lymphatic tissue of the palatine tonsils, organs of the urinary system, skin and soft tissues [4].The recommended treatment regimen with josamycin is 500 mg 3 times a day for 7-10 days. This drug is characterized by proven efficacy against chlamydia, ureaplasma and mycoplasma infections of the urogenital tract, as well as a favorable safety profile (absence of pathological effects on intestinal motility and microflora, minimal risk of drug interactions).During treatment, it is necessary to refrain from sexual intercourse (in extreme cases, it is necessary to use a condom), follow a diet that excludes the use of spicy, salty, fried, spicy and other irritating foods, as well as alcohol. Two weeks after the end of antibacterial therapy, the first control analysis is performed. If the result is negative, another follow-up analysis is performed a month later.The methods of prevention of ureaplasmosis do not differ from the methods of prevention of sexually transmitted diseases. First of all, it is the use of a condom during sexual intercourse and the avoidance of casual sexual intercourse [1, 5].

Conclusions:: Thus, the choice of an antibiotic for ureaplasma infection should be based on the results of microbiological studies of female genital discharge. Improving diagnostic tests to identify both specific and non-specific pathogens will allow achieving maximum results of antibacterial therapy in this category of patients. Timely administration of Vilprafen makes it possible to cure ureaplasmosis in 97.5% of cases. The high clinical efficacy of Vilprafen determines the high importance of this antibiotic for the treatment of sexually transmitted diseases.

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