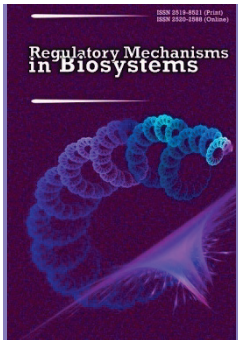

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Comparative analysis of etiological factors of infectious urocystitis of dogs and cats

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Worldwide, urocystitis is the most common disease of the urinary system. Urocystitis is a generalized name, since the disease has a varied etiology and can be complicated by bacterial microflora, passing from a non-infectious pathological process to an infectious one. Often, during the course of urocystitis, bacteria play the role of a complicating factor or are the primary cause of infectious urocystitis in dogs and cats. It should be noted that various pets can suffer from urocystitis, regardless of their age and sex. Therefore, the study of the causes of the disease among domestic animals, its etiology and degree of spread plays an important role in veterinary science. Identification of pathogens that most often provoke infectious urocystitis with the determination of their sensitivity to antibacterial agents is the key to successful treatment of this disease. Postmortem examination of small animals suffering from bacterial urocystitis showed that the pathological process was present in the urethra and bladder. Pathomorphological changes were characterized by purulent-catarrhal inflammation of the bladder with hemorrhages on its mucous membrane. The wall of the urethra was thickened, the mucous membrane was soaked with diffuse hemorrhages, and urethra was filled with hemorrhagic exudate. In order to find out the percentage ratio of infectious and non-infectious urocystitis, to identify microbial cells, to determine the species composition of the microflora and its sensitivity to antibiotics of different groups, aseptic urine samples were taken from animals with urocystitis. The study was conducted on 82 sick cats and dogs. The percentage of animals studied: 67% were dogs and 33% were cats. Urine collected by cystocentesis was subjected to microscopy and it was sown on nutrient media. Microscopy results showed the presence of bacteria of different shapes and concentrations in the urine of the sick animals. Of all the studied samples, 70.7% had no growth on nutrient media, which indicates the sterility of the studied urine while 29.3% showed bacterial growth when cultured on dense nutrient media (MPA, MPB and blood agar). In the process of microbiological research, the growth of six cultures of microorganisms was revealed, including: *Enterococcus* spp. (33.3%), *Escherichia coli* (29.2%), *Corynebacterium urealyticum* (12.5%), *Staphylococcus* spp. (12.5%), *Proteus* spp. (8.3%), *Staphylococcus haemolyticus* (4.2%). The obtained pure cultures were cultured on the selective Muller-Hinton medium in order to determine their antibiotic resistance. It was established that bacterial agents show the greatest sensitivity to fluoroquinolone antibiotics (enrofloxacin, ofloxacin, ciprofloxacin), cephalosporins (cefazalin, cephalexin, and ceftriaxone) and nitrofuran derivatives (furomag, furagin) on the Muller-Hinton medium.

Keywords: urine; cystocentesis; microbiological studies; bacteria; antibiotics.

Introduction

Diseases of the urinary system are relevant for cats and dogs, because they occur regardless of the age of the animal or the season. Among all pathologies of the urinary system of small animals, urocystitis is the most common. Cats and dogs tend to suffer from this pathology both at a young and at a geriatric age. It should be noted that cats get sick more often than dogs, because for cats a complicating factor for the occurrence of urocystitis is that up to 22% of cats are sick with urolithiasis (Hostutler et al., 2005; Kaul et al., 2020; Mylostyvyi et al., 2023). In veterinary practice, urocystitis is considered as a generalized concept that characterizes the inflammatory process localized in the urethra and bladder. However, depending on the cause of origin, it is divided into idiopathic and infectious. The vast majority of clinical cases in cats and dogs is due to idiopathic urocystitis, which occurs against the background of urolithiasis, chronic kidney diseases, and even under conditions of stress (Karpenko et al., 2022; Sameliuk et al., 2022; Martyshuk et al., 2022). Due to the specificity of the anatomical structure, females suffer from urocystitis more often than males, since the female urethra is wider and shorter (Wan et al., 2014).

Idiopathic urocystitis can become bacterial if bacteria penetrate the inflammatory process (Sparkes, 2018). The cause of infectious urocystitis is considered to be complications of accompanying pathologies, including: pyometra, megacolon, immunodepressive state of the body. Under these circumstances, the urethra performs the function of the "gateway of infection", through which pathogenic microflora enters the bladder to an already existing non-infectious pathological process or primarily provokes the emergence of infectious urocystitis. Therefore, urocystitis is a more accurate definition, since bacterial inflammation of the urinary bladder is impossible without prior infection of the urethra (Sævik et al., 2011; Weese et al., 2019). Bacterial urocystitis from a disease that occurs as a complication of another pathological process can pose a threat to the life of a sick animal, as its consequence is urosepsis (Guliciuc et al., 2021). In many clinical cases, secondary bacterial urocystitis becomes dominant in the complex of pathophysiological changes that occur in the patient's body. According to literature data, bacterial urocystitis accounts for approximately 5% of all clinical cases (Keay & Warren, 2002; Kaul et al., 2020).

Often, idiopathic and infectious urocystitis do not differ in characteristic clinical symptoms. Therefore, in addition to anti-inflammatory agents, systemic antibacterial drugs are prescribed to patients in complex therapy (Buffington, 2011; O'Neil et al., 2013). Laboratory diagnostics are also not always carried out using microscopic and bacteriological research methods due to the technical complexity of aseptic sampling of material for research. Therefore, when it comes to suspicion of infectious urocystitis, microscopy and urine culture on dense nutrient media are most often performed under the condition that first-choice antibiotics do not give the desired therapeutic effect. Such antibiotics include drugs from the group of nitrofurans (furagin, furomag, furazolidone, nitroxoline), because they have a bactericidal and bacteriostatic effect on gram-positive, gram-negative and unicellular microorganisms (Joosten et al., 2020). The bacteriostatic effect of nitrofuran derivatives consists in blocking the cycle of tricarboxylic acids in microbial cells and inhibiting the activity of dehydrogenase enzymes, while the bactericidal effect is provided by their ability to suppress respiratory cycles in cells of microorganisms and disrupt protein synthesis in cells of pathogenic bacteria. During their use, nitrofurans are concentrated in the largest amount in the gastrointestinal tract and urinary system, which determines their primary use in bacterial lesions of these systems. Analysis of the frequency of infectious urocystitis in small animals, the percentage ratio in dogs and cats, the criteria for determining the main infectious agents and the selection of appropriate effective antibiotics are the keys to minimizing the duration of treatment and suppressing the symptoms of the inflammatory process, as well as preventing the transition of the disease from an acute state to a chronic one.

At the Department of Normal and Pathological Morphology and Forensic Veterinary Medicine of the Lviv National University of Veterinary Medicine and Biotechnology named after Stepan Gzhitskyi, autopsies were performed on animals diagnosed with bacterial urocystitis during their lifetime. According to the owners, at the beginning of the treatment, the dead animals received broad-spectrum antibiotics, and already in the absence of positive dynamics, the doctors performed cystocentesis and microbiological studies of urine. The obtained results became the reason for further research on the identification of the main causative agents of the disease and their sensitivity to antibacterial drugs. For this purpose on the basis of the veterinary clinic "Merlion" of the city of Lviv, microscopic and bacteriological studies of urine of cats and dogs with urocystitis were carried out during the year, where culture was used in the diagnostic process to determine its sterility. The research material was urine, which was collected by cystocentesis in each clinical case. The frequency of occurrence of bacterial urocystitis in comparison with idiopathic ones and the percentage ratio of this pathology in dogs and cats were determined. Microscopy of urine sediment and sowing it on dense nutrient media made it possible to identify and isolate the pathogen that caused bacterial urocystitis in sick animals, as well as the sensitivity of the obtained culture of the pathogen to antibiotics of different groups. Therefore, an important aspect is conducting complex diagnostics before using any medications, which includes: taking a detailed history, conducting biochemical and hematological blood analysis, biochemical, microscopic and microbiological analysis of urine sediment, ultrasound examination (Shulzhenko et al., 2019). A wide-spectrum diagnostic approach to each patient provides an opportunity to establish an accurate diagnosis of bacterial urocystitis, based on etiological, pathomorphological and bacteriological factors that contributed to the emergence of this pathology (Wong et al., 2015). Based on the received research data, a veterinarian can estimate the frequency of infectious urocystitis in dogs and cats, get acquainted with the percentage of pathogens and choose the most effective antibiotics that should be used for treatment according to the results of the antibiotic chart.

The goal of the work – to investigate the percentage ratio of infectious and non-infectious cases of urocystitis, to establish microscopic changes in urine during the course of bacterial urocystitis, to determine the species composition of the microflora and its sensitivity to antibiotics of different groups in dogs and cats.

Materials and methods

Autopsies of corpses were carried out at the Department of Normal and Pathological Morphology and Forensic Veterinary Medicine of the Stepan Gzhytskyi Lviv National University of Veterinary Medicine and Biotechnology according to the generally accepted method of autopsy of corpses and the corresponding general scheme (Horalskyi et al., 2005).

In order to obtain urine uncontaminated by bacteria or cells from the distal genitourinary tract, diagnostic urine samples were taken by cystocentesis. Cats and dogs of small breeds were fixed in a supine position with an inclination. The location of the bladder was palpated with fingers and pressed against the side wall with one hand so that there were no other internal organs between them. In large dogs, bladder puncture was performed in the supine position under ultrasound control. An ultrasonic device "MyLab 30" by ESAOTE S.p.A. was used for control – Via Siffredi 58 – 16153 Genova – Italy. The cannula of the syringe was pierced through the abdominal wall in the direction of the bladder neck. This excluded the possibility of its slipping out during gradual emptying and the need for repeated puncture (Meire et al., 2001; Tanagho & McAninch, 2004). As long as the cannula was in the lumen of the bladder, it was not pressed so that urine did not enter the abdominal cavity through the puncture channel. In this way, urine was obtained for its further inoculation on dense nutrient media without harming the organism of sick animals.

Urine microscopy was performed using the native method. Urine was centrifuged in a centrifuge tube for 5 minutes at 2000 revolutions per minute. A drop of urine taken from the bottom of the test tube was placed on a glass slide and microscopy was performed under magnification with a small ($^{X}10$) microscope objective. A MICROmed XS-5520 microscope was used for urine sediment microscopy.

Bacteriological studies of urine were carried out in the microbiological laboratory "MotaLab" of the city of Lviv (License for conducting economic activities for medical practice Order of the Ministry of Health No. 127 dated 25.01.2018) by the method of cultures on dense nutrient media (MPA, MPB and blood agar). Urine was applied in the form of strokes with the help of a bacteriological loop on the surface of a dense nutrient medium, which was poured into Petri dishes. In order to optimize the process, several nutrient media were poured into the cup, having previously divided the bottom of the cup into sectors. A small amount of the studied material was collected with a sterile loop, rubbing it into the surface of the medium, moving away from the edge of the cup. Next, the loop was flambéed over the flame of the still, and then cooled. Sowing continued from the area where the previous one ended in such a way that strokes were made from edge to edge of the cup, being placed close to each other, but without damaging the surface of the medium. Thanks to the manipulations, the conditions for obtaining isolated colonies were ensured. The cups were placed in a thermostat at a temperature of 37 °C for 20–24 hours (Matuschek et al., 2014).

Cultivation of urinary tract on meat-peptone broth, meat-peptone agar and blood agar.

Preparation of MPB: 20 g of finely chopped agar agar was added to 1 liter of meat-peptone broth and the medium was heated until the agar dissolved. A slightly alkaline reaction was established with a 20% Na_2CO_3 solution and poured into a column 5 mm high. Tubes with medium were sterilized in an autoclave at 120 °C for 20 minutes.

Preparation of MPA: 1% peptone was added to 100 mL of broth to increase the nutrient content of the medium. For compaction, 2% agar was added. In order to create a slightly acidic pH, 0.5% table salt was added to the medium (the reaction of the resulting medium was from 7.0 to 7.4). After adding agar, the mixture was heated until incomplete solidification. The resulting medium was poured into Petri dishes with a height of 5 mm.

Preparation of blood agar 10% of defibrinated horse blood was added to the meat-peptone agar at the solidification stage when the temperature was below 50 °C. The resulting medium with a pH of 6.8 was poured into Petri dishes. Then it was autoclaved at a temperature of 80 °C for 15 minutes (Shyrobokov, 2011).

The resulting pure culture was transplanted onto Muller-Hinton agar in order to determine the sensitivity of the pathogen to antimicrobial agents using the disk diffusion method. When determining sensitivity by the disk diffusion method, a standard inoculum corresponding to 0.5 according to the McFarland standard was used, that is, it contains approximately 1.5×10^8 colony-forming units per cubic centimeter. The inoculum was applied with a pipette to the surface of the Petri dish in a volume of 1–2 cm^3, distributing it evenly, and removing the excess with a pipette. Petri cups were dried at room temperature for 10–15 minutes and discs with antibiotics were placed on the surface of the nutrient medium (Mueller & Hinton, 1941).

In the process of work, discs impregnated with antibiotic solutions produced by LLC "Aspect" Ukraine were used. The content of antibiotics in the disks corresponds to the recommendations of WHO and TU U 24.4-21615987-001:2009. Application of discs was carried out using sterile tweezers, keeping a distance of 15–20 mm from the disc to the edge of the cup. Immediately after the application of the disks, the Petri dishes were placed upside down in a thermostat and incubated at a temperature of 35 °C for 18–24 hours.

Results

Autopsy of the corpses of animals that suffered from bacterial urocystitis during life showed the presence of pathomorphological changes in the bladder and urethra, which were characterized by purulent cystitis and hemorrhagic urethritis (Fig. 1a). It was found that the bladders were enlarged, filled with cloudy urine with serous-purulent exudate. The mucous membrane was swollen, with numerous dotted and spotted hemorrhages (Fig. 1b). The urethra of the dead animals had a thickened wall, a swollen mucous membrane with hemorrhages, which were impregnated with hemorrhagic exudate (Fig. 1c). The research on 82 animals showed that urocystitis was diagnosed in 55 cats (67%) and 27 dogs (33%, Fig. 2). The percentage ratio of infectious and non-infectious urocystitis was 29.3% and 70.7%, respectively (Fig. 3). This is evidenced by the absence of bacterial growth on nutrient media in 70.7% of the studied urine samples while the growth of bacteria in the rest (29.3%) indicated the presence of a diagnosis of infectious urocystitis in the studied animals, since the urine was collected by an aseptic method, which excluded its secondary insemination.

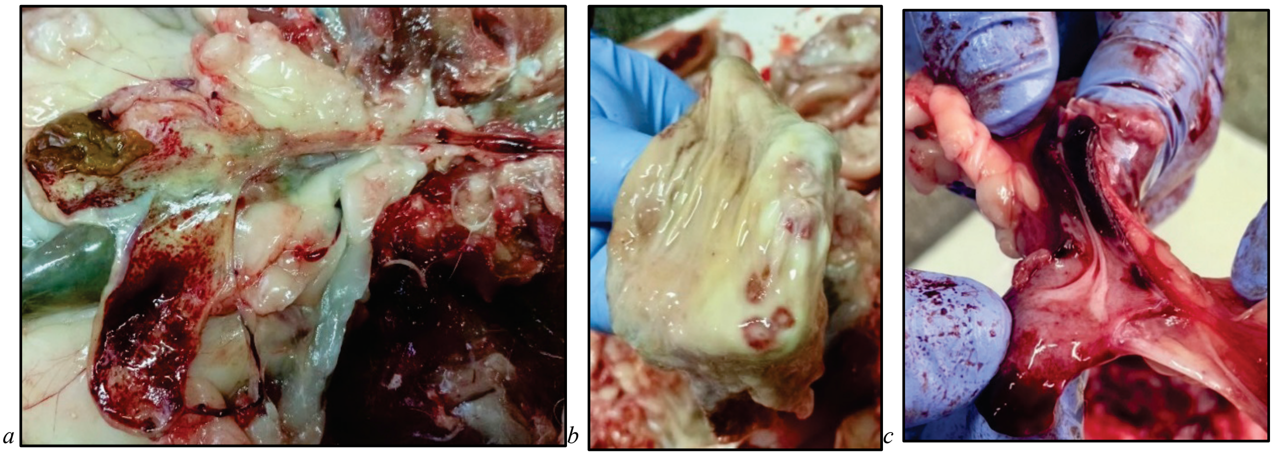

Fig. 1. Postmortem examination: *a* – purulent urocystitis and hemorrhagic urethritis; *b* – purulent cystitis; *c* – hemorrhagic exudate in the thickness of the urethra; thickening of the urethral wall

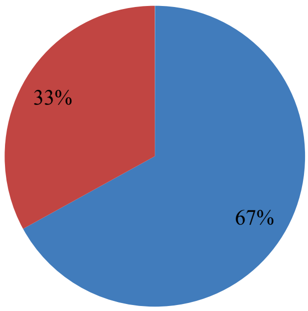

Fig. 2. Number of animals with urocystitis: ■ – cats; ■ – dogs

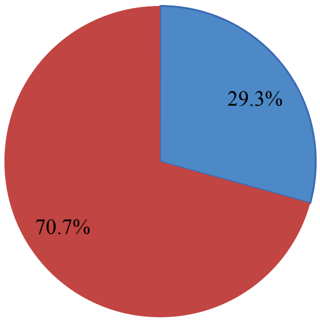

Fig. 3. Correlation infectious and non-infectious urocystitis: ■ – microflora growth is present; ■ – there is no growth of microflora

It should be noted that infectious urocystitis in dogs prevailed in females (8 animals out of 12), and in cats in males (9 animals out of 12), which can be explained by the specificity of the pathogenesis of the disease in these types of animals. Female dogs are more prone to the occurrence of infectious urocystitis, since in them the causative agent most often enters the body from the environment through a short, wide urethra. In cats, a favorable factor for infectious urocystitis is that they often suffer from recurrences of urolithiasis, which is characterized by difficult, painful and frequent urination.

Urine freshly collected by cystocentesis was subjected to microscopy. Microscopy of urine sediment in sick animals showed the presence of coccal microflora or rods in the field of view of the microscope. At the same time, the number of bacteria in the studied material was different. In some samples, bacteria were visualized singly, and in order to detect them, it was necessary to view several slides whereas in other samples the entire field of view of the microscope was covered with bacterial cells (Fig. 4). Regardless of whether bacterial microflora was detected in the urine under microscopy, each sample obtained was subjected to bacteriological examination in order to find out the species composition of the microflora and determine its sensitivity to antibiotics. The method of native microscopy makes it possible to detect bacterial cells only under the condition of aseptic sampling of the material for research. However, it is impossible to reliably establish the type of bacteria with this method, and even more so to prescribe one or another type of antibiotic. Its addition is the conduct of bacteriological studies, which directly establish the presence or absence of a specific pathogen and enable the veterinarian to prescribe, according to the results of the antibioticogram, a drug that will be effective against a specific type of bacteria.

Bacteria of the genera *Corynebacterium*, *Enterococcus*, Enterobacteriaceae and *Staphylococcus*, namely *Enterococcus* spp., were found in urine during bacteriological examination on MPA, MPB and blood agar nutrient media (33.3%), *Escherichia coli* (29.2%), *Corynebacterium urealyticum* (12.5%), *Staphylococcus* spp. (12.5%), *Proteus* spp. (8.3%), *Staphylococcus haemolyticus* (4.2%, Fig. 5).

To determine the antibiotic resistance of the obtained cultures, disks with antibiotics of different groups were used, namely: penicillins, cephalosporins, fluoroquinolones, antibiotics of the tetracycline series and aminoglycosides, in particular: azithromycin, amoxicillin, amoxiclav, gentamicin, doxycycline, metronidazole, ofloxacin, furagin, furomag, cefazolin, ceftriaxone and ciprofloxacin. Antibiotics that are widely used in practical veterinary medicine today were chosen for the study. The results of the research showed (Table 1) that the obtained microorganisms are most sensitive to antibiotics of the cephalosporin group: ceftriaxone – 70.8% of the samples, cefazolin – 45.8% and the fluoroquinolone series, in particular ciprofloxacin and ofloxacin, to which 62.5% showed sensitivity of studied samples. From the group of antibiotics of the furazolidone series, the obtained microorganisms were most sensitive to furomag (54.1%).

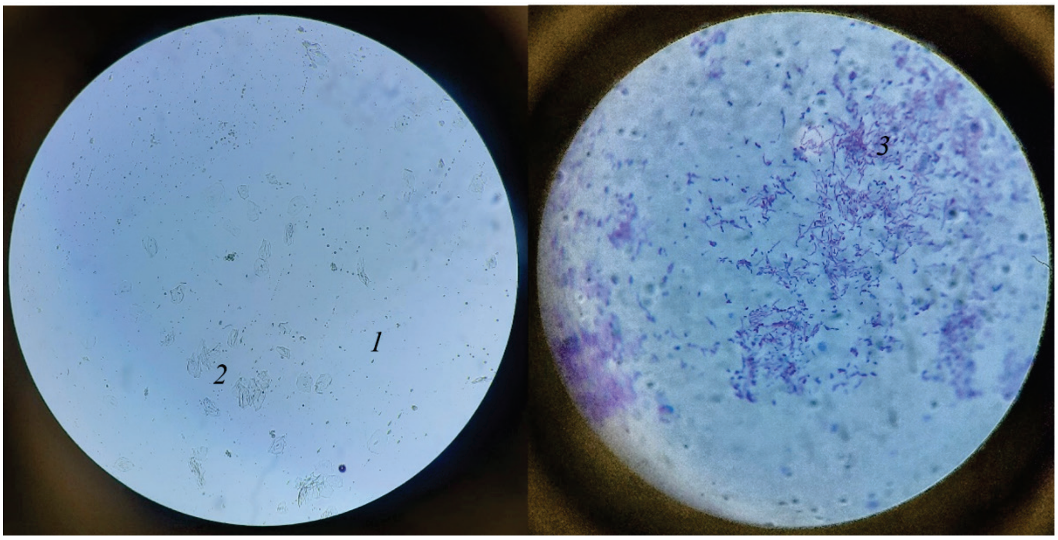

Fig. 4. Microscopy of urine sediment ($^{X}10$): *1* – single coccal microflora; *2* – fragments of the epithelium; *3* – bacilli in large numbers

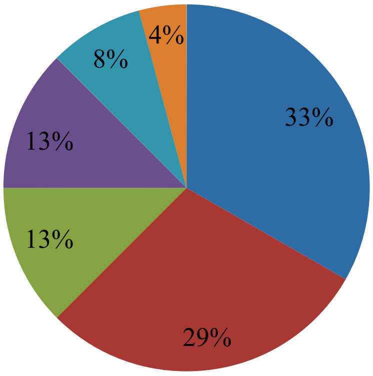

Fig. 5. Cultures obtained during the cultivation of urine (%):
– *Enterococcus* spp.; – *Escherichia coli*;
– *Corynebacterium urealyticum*; – *Staphylococcus* spp.;
– *Proteus* spp.; – *Staphylococcus haemolyticus*

Discussion

The issue of infectious urocystitis is relevant for small animals, as the disease occurs in both cats and dogs. Urocystitis of infectious and non-infectious origin is characterized by the same clinical manifestation. Typical symptoms of urocystitis are frequent, painful urination with the release of small portions of urine. During the course of the disease, animals become restless and often try to lick the distal part of the urogenital canal, because they feel discomfort due to the course of inflammation (Kullmann et al., 2018). Given the typical manifestations of the disease and the obviousness of the diagnosis of urocystitis, veterinarians often ignore cystocentesis, which is performed to collect material for bacteriological research. This is explained by the technical complexity of this manipulation, which does not cause any harm to the animal. Therefore, the generalization of the studies conducted on this pathology is mainly based on the results of sowing urine on dense nutrient media after primary therapy, provided that it does not give the desired positive results.

Therefore, as a result of untimely treatment with antibiotics, to which there are insensitive bacteria that cause infectious urocystitis, often irreversible pathological changes occur in the bladder and urethra (Forrest & Dell, 2007). During the long course of bacterial urocystitis, due to the accumulation of purulent exudate, which contains fibrin, the outflow of urine becomes difficult (Halder et al., 2016). In such conditions, uropathogens have the opportunity to multiply in greater numbers and complicate the course of an already existing pathological process (Behzadi, 2020). Purulent cystitis in combination with hemorrhagic urethritis leads to urosepsis (Guliciuc et al., 2021). Therefore, it is important to establish not only the type of bacteria that caused infectious urocystitis, but also to establish their sensitivity to antibacterial drugs at the stage of early diagnosis (Marques et al., 2016). And if it is impossible to carry out cystocentesis, it is necessary to prescribe antibiotics that will be most effective against the bacteria (Zazharskyi et al., 2019; Buckingham et al., 2023; Duzhyi er al., 2023; Fares et al., 2023).

Table 1
Antibiotic resistance of the obtained pure cultures (%)

Antibiotic	Urine microflora		
	sensitive, %	moderately stable, %	resistant, %
Azithromycin	29.2	16.7	54.1
Amoxicillin	25.0	29.2	45.8
Amoxiclav	29.2	8.3	62.5
Gentamicin	33.0	12.5	54.5
Doxycycline	50.0	12.5	37.5
Metronidazole	20.8	12.5	66.7
Ofloxacin	62.5	4.2	33.3
Furagin	37.5	16.7	45.8
Furamag	54.1	8.3	37.6
Cefazolin	45.8	8.3	45.9
Ceftriaxone	70.8	12.5	16.7
Ciprofloxacin	62.5	8.3	29.2

That is, for the treatment of bacterial urocystitis, antibiotics of a wide spectrum of action are used, and if there are no positive dynamics during therapy, a urine culture should be carried out in order to establish the specific pathogen and determine its sensitivity to antibiotics. But this approach is uninformative, because if antibiotics are previously used, bacteria develop resistance not only to the antibiotic chosen by the doctor, but also to others that are weaker than it in terms of spectrum of action (Sævik et al., 2011). It is also necessary to take into account concomitant factors affecting animals with urocystitis, which can cause the transition from non-infectious to infectious urocystitis (Ishii et al., 2011). These factors include: pyrometra in females, urolithiasis in cats, development of megacolon and diarrhea due to pathologies of the digestive system (Weese et al., 2011). A separate group includes idiopathic urocystitis, which have an unknown pathogenesis. The most common causes include stress, estrus in females and adverse reaction to a number of medications (Wan et al., 2014). There are also publications that indicate that today idiopathic urocystitis is the norm for small breed dogs and cats, which are the most stress-sensitive (Seawright et al., 2008; Barsanti, 2012). Therefore, all the listed factors always create a risk for the occurrence of infectious urocystitis.

It is important not to forget that correct comprehensive diagnosis is the key to effective treatment (Byron, 2019). In the case of bacterial urocystitis, the first and most important stage of diagnosis is the correct collection of material for examination. Only the examination of urine collected by an aseptic method makes it possible to accurately confirm or refute the diagnosis of bacterial urocystitis, since contamination with secondary microflora is unacceptable (Gordon, 1990; Tanagho & McAninch, 2004). Microscopy of the urine sediment makes it possible to establish the presence of pathological inclusions in the urine. These include: bacteria, struvite or oxalate crystals, mucus and atypical cells (Tanagho & McAninch, 2004). The method of native microscopy makes it possible to detect bacterial cells only under the condition of aseptic sampling of the material for research. However, it is impossible to reliably establish the type of bacteria with this method, and even more so, it is impossible to prescribe one or another type of antibiotic (Weese et al., 2019). Microscopy is only one of the steps in the staged diagnosis of bacterial urocystitis. The next step is to conduct bacteriological studies which directly establish the presence or absence of a specific pathogen and enable the veterinarian to prescribe a drug that will be effective against a specific type of bacteria in accordance with the results of the antibioticogram. Therefore, to generalize the results of the research we obtained, antibiotics were chosen, which today are the most widely used by veterinary specialists all over the world (Litster et al., 2009; Yu et al., 2020). The study made it possible to generalize and display in percentage terms the frequency of infectious urocystitis in comparison with non-infectious urocystitis, to establish the most common bacterial pathogens in urocystitis and the ways of their elimination through the use of antibiotics to which this microflora is most sensitive.

Conclusions

During the course of bacterial urocystitis, the accumulation of serous-purulent and hemorrhagic exudate in the bladder and urethra was noted. Every third animal (33%) with urocystitis had a presence of bacterial growth in cultures of its urine, which was collected aseptically. The growth of a colony of *Enterococcus* spp. was most often observed in urine cultures (33.3%). The studied microflora shows the greatest sensitivity to fluoroquinolone antibiotics, cephalosporins and nitrofurans.

The authors declare that no conflict of interest exists.

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