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UROSEPSIS. PATHOGENESIS, DIAGNOSIS AND TREATMENT

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Modern data on terminology, classification, pathogenesis, diagnostics and treatment of urosepsis were presented in clinical lecture. Particular attention is paid to laboratory and clinical criteria for assessing the severity and prognosis of the disease, as well as methods for preventing urosepsis.

Keywords: urosepsis; biomarkers; antibiotic therapy.

УРОСЕПСИС. ПАТОГЕНЕЗ, ДИАГНОСТИКА И ЛЕЧЕНИЕ

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В клинической лекции представлены современные данные о терминологии, классификации, патогенезе, методам диагностики и лечения уросепсиса. Особое внимание уделено лабораторным и клиническим критериям оценки тяжести и прогноза заболевания, а также методам профилактики уросепсиса.

Ключевые слова: уросепсис; биомаркеры; антибактериальная терапия.

INTRODUCTION

Sepsis is a life-threatening multisystemic failure caused by the body's unregulated response to infection [1]. Sepsis treatment continues to be a challenging issue of the 21st century, necessitating a multidisciplinary approach to managing it. Sepsis ranks 11th among all causes of death in adults, and in developed countries, an increased sepsis frequency has been noted, at an average of 7%–8% annually [2, 3].

Notably, sepsis is classified based on various criteria, such as the nature of the course (peracute, acute, subacute, chronic, recurrent), the characteristics and localization of the site of entry (wound, burn, abdominal, obstetric-gynecological, angiogenic, urosepsis, biliary, pulmonogenic, catheter-associated, umbilical, cryptogenic), and etiological signs (gram-negative, gram-positive, staphylococcal, streptococcal, colibacillary, pseudomonal, viral, fungal).

The most widely used classification is the American College of Chest Physicians/Society of Critical Care Medicine (ACCP/SCCM), based on the severity of the body's response to an infectious process [4]. This classification, for the first time, proposed to use the term "systemic inflammatory response syndrome" (SIRS), which is a body's systemic reaction to strong stimuli (infection, trauma, surgery, etc.). This classification is presented in Table 1.

Urosepsis is a life-threatening organ dysfunction caused by dysregulation of the response to the urinary tract or male genital infections [1]. Urosepsis holds a specific place among various types of sepsis

Table 1 / Таблица 1

Classification and diagnostic criteria for septic lesions ACCR/SCCM [4]
Классификация и критерии диагностики септических поражений ACCP/SCCM [4]

Septic lesion	Clinical and laboratory criteria
Systemic inflammatory response syndrome	It is characterized by two or more of the following signs: • body temperature higher than 38 °C or lower than 36 °C; • heart rate higher than 90/min; • respiratory rate higher than 20/min or hyperventilation ($PaCO_2$ <32 mmHg); • blood leukocytes >12 × 10^9/ml or <4 × 10^9/ml or immature forms >10%
Sepsis	Presence of a focus of infection and two or more signs of systemic inflammatory response syndrome
Severe sepsis	Sepsis associated with organ dysfunction, hypotension, tissue perfusion disorders. The latter is manifested by an increase in lactate levels, oliguria, acute impairment of consciousness
Septic shock	Severe sepsis with signs of tissue and organ hypoperfusion, arterial hypotension that is not correcting using fluid therapy and requires the administration of catecholamines
Additional definitions	
Multiple organ dysfunction syndrome	Dysfunctions of two or more systems or organs, determined based on the SOFA scale criteria
Refractory septic shock	Persistent arterial hypotension with systolic BP lower than 90 mmHg (mean BP <65 mmHg), despite adequate infusion, use of inotropic and vasopressor support

because of its specific qualities and high frequency. Urosepsis constitutes 31.4% of all clinical forms of sepsis, with two-thirds of patients being women [5]. In 25% of cases, urosepsis is a complication of acute pyelonephritis. In most cases of urosepsis, pathogens are representatives of the *Enterobacteriaceae* family, with *Escherichia coli* being the most frequent. Like other forms of sepsis, the disease severity is determined primarily by the state of the body's immune system.

The primary risk factors of urosepsis include obstruction of the urinary tract at any level, congenital uropathies, neurogenic bladder, and endoscopic interventions on the urinary tract. Elderly patients with diabetes mellitus or immunosuppression, and patients receiving anticancer chemotherapy or corticosteroids are at the highest risk of urosepsis. In addition, the following urological factors predispose to the development of purulent septic complications: 1) the use of artificial materials, such as drains, catheters, prostheses, sphincters, and slings, which leads to the development of biofilm infections and foreign body infections; 2) a change in the nature of urosurgical interventions and the introduction of high-tech minimally invasive methods, for example, lithotripsy instead of removing the stone entirely or layer-by-layer resection of the prostate instead of removal of hyperplastic nodes in a single block. During the fragmentation of stones, microorganisms and their toxins enter the urinary tract and enter the bloodstream under the pressure of the irrigation fluid or increased intrapelvic pressure. Consequently, toxemia, bacteremia, SIRS, and septic complications occur. Furthermore, during transurethral interventions on the prostate gland, endotoxins and microorganisms possibly enter the bloodstream under the pressure of irrigation fluid and trauma.

The *pathogenesis* of septic lesions is determined based on the complex and close interaction of the following three factors: the pathogenicity of the microorganism, the state of the primary focus of infection, and the body's immunoreactivity. The development of organ-systemic lesions in sepsis is primarily associated with the uncontrolled dissemination of pro-inflammatory mediators of endogenous origin from the primary focus of infectious inflammation, followed by their activation in other organs and tissues, with the secondary release of similar endogenous substances, damage to the endothelium, and a decrease in organ perfusion and oxygen delivery. Dissemination of microorganisms may be absent or be short-term. The cumulative effects of mediators cause SIRS. Notably, there are three main stages in its development.

Stage 1. Local production of cytokines in response to the action of microorganisms.

The cytokine network holds a special place among the mediators of inflammation because it controls the implementation of immune and inflammatory reactivity processes. Cytokines initially act at the focus of inflammation and on the territory of the reacting lymphoid organs, eventually performing several protective functions, participating in the processes of wound healing and protecting body cells from pathogenic microorganisms.

Stage 2. Release of a small number of cytokines into the systemic circulation.

Small amounts of mediators can activate macrophages, platelets, the release of adhesion molecules from the endothelium, and the production of growth hormone. Therefore, maintaining a balance and controlling the relationship between pro- and anti-inflammatory mediators under normal conditions would provide the prerequisites for wound healing, destruction of pathogenic microorganisms, and maintenance of homeostasis. Systemic adaptive changes during acute inflammation include stress reactivity of the neuroendocrine system, fever, release of neutrophils into the general blood flow from the vascular and medullary depots, increased leukocytopoiesis in the bone marrow, hyperproduction of acute-phase proteins in the liver, and the development of generalized forms of the immune response.

Stage 3. Generalization of the inflammatory response.

Notably, some cytokines can enter the systemic circulation and accumulate in quantities sufficient to implement their effects during severe inflammation. In the case of inability of regulatory systems to maintain homeostasis, the destructive effects of cytokines and other mediators start to prevail, which causes impaired capillary endothelial permeability and function, triggering disseminated intravascular coagulation syndrome, the formation of distant foci of systemic inflammation, and the development of mono- and multisystemic dysfunction. Dysfunctions of the liver, kidneys, and intestines contribute to the emergence of new lesional factors, such as high concentrations of products of normal metabolism (lactate, urea, creatinine, bilirubin), mediators of regulatory systems (kallikrein-kinin system, coagulation system, fibrinolytic system, lipid peroxidation, neurotransmitters), and products of impaired metabolism (aldehydes, ketones, higher alcohols).

LABORATORY CRITERIA OF SEPSIS

The criteria for SIRS include changes in the clinical blood test, namely leukocytosis of greater than 12×10^9/L, leukopenia of lower than 4×10^9/L, or a shift toward immature forms (>10%) with a normal leukocyte count [4]. Moreover, the blood levels of bilirubin increase above 20 μmol/L within two days or transaminase levels increase two times or more from the norm [6]. Furthermore, in severe sepsis, thrombocytopenia, blood clotting disorder (INR >1.5, PTT >60 s), hyperbilirubinemia at least 34.2 μmol/L, increased lactate level greater than 2 mmol/L, and hypercreatininemia higher than 176.8 mmol/L have been registered with the above criteria [6, 7].

Biological markers (biomarkers) of sepsis are crucial in the diagnostics and assessment of sepsis severity. These markers are the molecular, biochemical, or cellular indicators determined in the biological media, such as tissues, cells, or fluids. Biomarkers need to possess unique properties, namely high sensitivity and specificity, availability, rapidity of results, reproducibility, and ability to correlate value with severity and outcome.

The key biomarkers of sepsis are procalcitonin, C-reactive protein, and presepsin.

Procalcitonin (PCT) is a precursor of the hormone calcitonin and is represented by a polypeptide with a molecular weight of approximately 14.5 kDa, consisting of 116 amino acid residues. Normally, PCT is formed in the C cells of the thyroid gland, where it is almost completely transformed into calcitonin because of specific intracellular proteolytic cleavage. Therefore, only trace PCT concentrations (<0.05 ng/ml) are detected in blood plasma in healthy people [8]. PCT has a significantly longer plasma half-life (22–35 h) than calcitonin (10 min). In severe bacterial infections and sepsis, PCT can be synthesized in leukocytes, as well as in neuroendocrine cells of the lungs, intestines, and liver [8].

An increase in PCT concentration higher than 2 ng/ml is a specific biological marker in severe bacterial infections and sepsis. PCT concentrations higher than 10 ng/ml are registered almost exclusively in patients with severe sepsis and septic shock. In fungal and viral infections, as well as in allergic

and autoimmune diseases, the PCT level does not significantly increase, which facilitates the use of this marker for differential diagnostic purposes. In local inflammation, PCT release is typically much less pronounced, enabling the use of this marker to assess the degree of the process generalization [8]. The generalization of infection is characterized by a rapid, within several hours, an increase in the PCT level wherein the blood plasma concentration can reach extremely high values (>500 ng/ml). In the case of effective treatment, the PCT level decreases and normalizes. Nonetheless, with inadequate therapy, the PCT level remains high or increases further, which warrants an immediate revision of the antibiotic therapy regimen and, possibly, additional treatment methods. In some cases, the dynamics of PCT levels suggest assessing the patient's condition to a greater extent than its absolute values. If the PCT level decreases by 30% or more per day during treatment [9], the therapy can be considered effective. However, daily monitoring of the PCT level is required to assess the patient's condition and choose an adequate therapeutic approach in patients with infection or a high risk of its development.

Nevertheless, those clinical conditions need to be considered that are not associated with the infectious process but exhibit increased PCT blood levels, such as neuroendocrine tumors, small cell lung cancer, carcinoid syndrome, and malaria. For example, after severe trauma and surgery, the blood concentration of procalcitonin increases rapidly, and, in the absence of infection, decreases and returns to normal after 3–5 days, during which it is impossible to confirm or exclude sepsis assertively based only on the procalcitonin [10].

Table 2 summarizes recommendations for the clinical interpretation of PCT test results.

C-reactive protein (CRP) belongs to the group of acute-phase proteins, has a molecular weight of 118 kDa, and consists of five subunits. CRP is synthesized predominantly in hepatocytes, and its inductors are proinflammatory cytokines, primarily the interleukin-6 [11]. After an infectious factor enters the body, the blood concentration of CRP increases rapidly (within 6–8 hours), doubles every 8 hours, and reaches its peak in 36–50 hours. After eliminating the pathogen, the CRP concentration decreases rapidly because of a half-life of 19 hours.

CRP is a widespread nonspecific biomarker of inflammation. The blood plasma level of CRP increases in bacterial, fungal, and viral infections, and in several non-infectious diseases, such as myocardial infarction, trauma, chronic inflammatory processes (rheumatoid diseases, systemic vasculitis, etc.), as well as after surgical interventions. The significant advantages of CRP include its broad availability and low cost, and the main disadvantage is its low specificity.

Table 2 / Таблица 2

Clinical interpretation of the results of the PCT test in cases of suspected severe bacterial infection and sepsis
Клиническая интерпретация результатов ПКТ-теста при подозрении на тяжелую бактериальную инфекцию и сепсис

PCT concentration, ng/ml	Clinical interpretation
<0.05	No bacterial infection
<0.5	The probability of systemic infection (sepsis) is low. Local bacterial infection is possible (without systemic signs). If the PCT level was determined too early after the onset of the bacterial process (typically earlier than 6 hours), the measurement should be repeated after 6–24 hours
0.5–2	High probability of local bacterial infection. Moderate risk of severe systemic infection (sepsis). Case follow-up of the patient and repeated determination of the PCT level after 6–24 hours are required
2–10	High probability of generalized bacterial infection (sepsis). Risk of severe sepsis or septic shock
>10	High probability of severe sepsis or septic shock

Notes. PCT – procalcitonin

Presepsin (PSP) is a 13 kDa protein – a soluble truncated form of the macrophage receptor protein CD14, sCD14-ST. The PSP level is significantly higher in patients with sepsis than those with nonspecific systemic inflammation or in healthy people. Normally, the blood level of PSP is in the range of 60.1–365.0 pg/ml [12]. Nonetheless, these values are approximate, and each laboratory should establish its PSP level reference. The advantages of PSP compared with the other proinflammatory biomarkers include an early increase in the level, clear indication of severity and dynamics of sepsis, the prognosis of recurrence, and outcome of sepsis [13].

MARKERS OF ORGAN DYSFUNCTION IN SEPSIS

The dysfunction of various organs or systems is a permanent component in sepsis. Markers, such as urea, creatinine, and bilirubin, are used to assess the severity of the condition and determine the prognosis.

One of the most crucial markers for assessing organ dysfunction is the *lactic acid* level (*lactate*) in venous blood. Normally, lactate is produced in erythrocytes, as well as in some tissues with a high level of glycolysis, even in the absence of tissue perfusion disorders. In this case, most of the lactate produced in the liver is converted back to glucose. Therefore, hepatic dysfunction, including that associated with sepsis, can cause a decrease in lactate clearance. Notably, hyperlactatemia is a common sign of sepsis and septic shock (sepsis-associated hyperlactatemia). In practice, a lactate level of 4 mmol/L or higher (with a norm of <2.0 mmol/L) is most often considered when diagnosing septic organ dysfunction. Currently, the diagnostics of sepsis-associated hyperlactatemia is recommended as a method to identify patients with latent shock, who require early targeted therapy. In addition, plasma lactate levels and their dynamics over time are reliable markers of the disease severity and mortality [14]. Patients with a lactate level of more than 4.0 mmol/L need management and treatment under intensive care unit conditions.

DIAGNOSTICS OF MULTIPLE ORGAN DYSFUNCTION

In 2016, at the International Congress III on diagnostics of sepsis and septic shock, the concept of "sepsis 3" was adopted. This concept implies the establishment of a diagnosis of sepsis in the presence of a confirmed infectious focus and organ dysfunction, which is recommended to be assessed using the sepsis-related organ failure assessment (SOFA) scale [15]. The SOFA scale was adopted with consensus at the conference of the European Society of Intensive Care Medicine in 1994 for assessment of sepsis-associated organ failure (Table 3). This scale helps quantify the severity of organ-systemic disorders.

Table 3 / Таблица 3

Clinical interpretation of the results of the PCT test in cases of suspected severe bacterial infection and sepsis

Клиническая интерпретация результатов ПКТ-теста при подозрении на тяжелую бактериальную инфекцию и сепсис

Organ/system	Indicator evaluated	Points			
			2	3	4
Oxygenation	PaO_2/FiO_2	<400	<300	<200	<100
Coagulation	Platelets, $\times 10^9$/л	<150	<100	<50	<20
Liver	Bilirubin, μmol/L	20–32	33–101	102–204	>204
Cardiovascular system	Hypotension or degree of inotropic support	SBP <70 mm Hg	Dopamine <5* or dobutamine (any dose)	Dopamine >5, or epinephrine <0.1 or norepinephrine <0.1	Dopamine >15, or epinephrine > 0.1, or norepinephrine > 0.1
Central nervous system	Glasgow coma scale score	13–14	10–12	6–9	<6
Kidneys	Creatinine, μmol/L, or volume of urine output	110–170	171–299	300–440 or 500 ml/day	>440 or <200 ml/day
Interpretation Minimum value SOFA = 0. Maximum value SOFA = 24. The more points a separate organ (system) has, the more pronounced its dysfunction. The higher the total score, the higher the degree of multiple organ failure.					

Note. * Doses of cardiotonics are indicated in mg/kg/min for at least 1 h. SBP – systolic blood pressure.

Table 4 / Таблица 4

Scale qSOFA (quick Sequential Organ Failure Assessment) [15]
Шкала полиорганной недостаточности, связанной с сепсисом, qSOFA [15]

Indicator	Points
Respiratory rate >22 per 1 min	1
Systolic BP <100 mmHg	1
Any impairment of consciousness	1

Note. 0 – mortality <1 %. 1 – mortality 2–3 %. ≥2 – mortality ≥10 %.

The disadvantage of the SOFA scale is the need for laboratory data (platelet, bilirubin, and creatinine counts, PaO_2), which precludes rapid assessment of the patient. Hence, a brief form of the scale called quick sequential organ failure assessment (qSOFA) (Table 4) is used in clinical practice successfully and has a high predictive value [15].

Furthermore, all diagnostic criteria for multiple organ failure from sepsis are applicable to its forms, including urosepsis.

MICROBIOLOGICAL DIAGNOSTICS OF SEPSIS

If sepsis is suspected in patients with urological disorders, it is imperative to perform blood and urine cultures with determination of microflora. In addition, in the case of surgical treatment, inoculation of discharge from drains and wounds is required.

The main indications for blood culture are

- hypothermia (body temperature lower than 36 °C) or fever (body temperature ≥38 °C);
- leukocytosis (>10,000 cells/mm^3);
- febrile neutropenia (fever ≥38 °C, neutrophils <1000 cells/mm^3).

The clinical significance of bacteremia consists the following:

- confirming the diagnosis and determining the etiology of the infectious process;
- obtaining evidence of the mechanism of sepsis development (for example, catheter-associated angiogenic infection);
- clarifying the severity of the pathological process in some clinical situations (for example, septic endocarditis, pyocyanin and Klebsiella infection);
- justification of the choice and change of the antibiotic therapy regimen;
- evaluation of the therapeutic effectiveness.

Nevertheless, bacteremia is not an absolute diagnostic criterion because even in the most severe patients, despite careful adherence to the blood sampling technique and the use of modern technologies to detect microorganisms, the frequency of positive blood culture results is 40%–60% [1, 16].

Notwithstanding, the culture should be sampled for inoculation before prescribing antimicrobial therapy, if it does not cause a significant delay (more than 45 minutes). Moreover, when performing a bacteriological study during antimicrobial therapy, blood sampling is performed immediately before the next injection of an antibiotic, that is, at the time of the lowest blood concentration of the drug. For an adult patient, a one-step sampling of 20 ml of blood, distributed in two vials, is optimal (a special medium for the isolation of anaerobes and fungi can be used). The required minimum sampling is two 10 ml samples (for adults) taken from the veins of different upper extremities at an interval of 30 minutes. Notably, three blood samples are optimal because it significantly increases the possibility of identifying the pathogen. Blood is sampled through the catheter if it is in the vein for less than 48 hours. When diagnosing a catheter-associated infection, samples from the vein and from the catheter are tested simultaneously.

When sampling blood, it is advisable to use standard vials with ready-made nutrient media, in which blood can be kept at room temperature for up to two days before cultivation in the laboratory. Nevertheless, blood cultures and unused vials must not refrigerated. Moreover, failure to comply with transportation rules can cause false-negative results when detecting microorganisms.

CRITERIA FOR ASSESSING THE CLINICAL SIGNIFICANCE OF POSITIVE HEMOCULTURE

The clinical significance of the bacteremia diagnostic results is assessed per the criteria developed

at the N.N. Blokhin Russian Cancer Research Center [17]. Per these criteria, all episodes of bacteriemia are divided into *significant* and *insignificant*.

Significant episodes include the following:

- Episodes of bacteremia from the microorganisms like *Escherichia coli*, *Klebsiella* spp., *Enterobacter* spp., and other members of the Enterobacteriaceae family; *Staphylococcus aureus*; yeasts and molds (excluding *Aspergillus* spp. and *Penicillium* spp.); *Pseudomonas aeruginosa* and other representatives of the group of non-fermenting gram-negative rods; and *Streptococcus* spp., with the exception of the viridans group. The growth of these microorganisms, noted even in a single blood culture during the day, should be considered of clinically significant.
- Episodes of bacteremia caused by microorganisms that typically represent the normal microflora of open human biotopes (skin and mucous membranes of the upper respiratory tract, gastrointestinal tract, etc.), or saprophytes (for example, coagulase-negative staphylococci, *Streptococcus viridans*, sporous gram-positive aerobic rod of the genus *Bacillus*, gram-positive cocci of the genus *Micrococcus*, fungi of the genera *Aspergillus* and *Penicillium*). Therefore, in the presence of the growth of such microorganisms (probable contaminants), multiple blood cultures are required, at least two times during the day with each episode of fever, to accurately interpret the results of microbiological examination. If the growth of such a microorganism is registered in at least two blood samples during the day, there is increased probability of the microorganism being the causative agent of infection, and not a contamination.

All other situations that may occur during a microbiological examination of blood are considered *insignificant episodes*. Growth of microorganisms-contaminants registered in only one of several vials can be confirmed as contamination that occurred while placing blood in the vial. Growth of microorganisms registered after a long period of incubation (more than 3–5 days) – the so-called delayed growth – is most probably a consequence of contamination (or colonization of the catheter). Furthermore, growth of different microorganisms noted in vials with the same blood sample is most probably a consequence of contamination during inoculation of blood into the vial or during manipulation of vials during inoculation in the laboratory. In addition, the group of insignificant episodes includes cases of bacteremia, wherein a single growth of microorganisms that typically represent the normal microflora of open human biotopes or saprophytes, is registered during the day. In such cases, it is extremely difficult to evaluate the result, and the probability of error is high.

Nevertheless, timely and accurate diagnosis of bacteremia can significantly decrease the frequency of unreasonable and inadequate prescription of antimicrobial drugs, which affect the therapeutic results of infectious complications in patients.

PRINCIPLES OF UROSEPSIS TREATMENT

Urosepsis treatment includes elimination of the cause (obstruction of the urinary tract, foci of infection), adequate measures to maintain vital functions, and adequate antibiotic therapy [18].

Elimination of urinary tract obstruction

One of the key components of urosepsis treatment strategy is eliminating any urinary tract obstruction and the removal of foreign bodies, in particular catheters, which itself can lead to symptom resolution. Notably, the choice of the method of urinary tract drainage depends on the causes of urodynamic disorders, as well as the stage and form of acute pyelonephritis, which is the most common cause of urosepsis.

Adequate drainage of purulent foci is one of the basic principles of urosepsis treatment. Therefore, in patients with serious condition, preference should be given to percutaneous drainage methods.

Antibacterial therapy

Initial empiric therapy should include broad-spectrum antibiotics or a combination of several antibiotics that initially cover the spectrum of possible pathogens. In the future, antibiotic therapy should be adjusted based on the results of bacteriological research.

The antibiotic therapy regimen should be selected considering several components, namely the infectious focus localization, the site of the infectious process, the level of antibiotic resistance, the medical case history, and the individual characteristics of the patient. In addition, in hospital sepsis, the presence or absence of risk factors and the involvement of bacteria with multiple resistances, such as *P. aeruginosa*, enterobacteria that produce

extended-spectrum beta-lactamase or carbapenemases (*E. coli*, *Klebsiella* spp.), and less often, bacteria of the genus *Acinetobacter*, should be considered.

Furthermore, antibacterial drug doses are of great significance in patients with sepsis, and should be high, except in patients with renal failure. Intravenous antibiotic therapy in patients with severe sepsis and septic shock should be started within the first hour after diagnostics and resolution of the urinary tract obstruction [19].

Table 5 presents the antibacterial drugs specified in the clinical guidelines of the European Association of Urology (2019) for treating urosepsis [20].

Fluoroquinolones are not the drugs of choice for empiric antibiotic therapy, given the high rates of resistance of microorganisms to this group of drugs, especially in patients hospitalized in urological departments, as well as those who have previously received drugs of this group over the preceding 6 months.

When choosing an antibacterial drug for treating patients with urosepsis, the type of pathogens and their level of antibiotic resistance should be considered first. First and second generation cephalosporins cannot chosen for empirical therapy of nosocomial urosepsis because of their insufficient activity against microorganisms, such as *Enterococci*, *Acinetobacter*, and *Pseudomonas aeruginosa*. Nevertheless, it is possible to treat with fourth-generation cephalosporins along with aminoglycosides or carbapenems with any suspected lack of sensitivity to other groups of antibiotics. If gram-positive sepsis is suspected, vancomycin is added to therapy. The use of fluoroquinolones and antipseudomonal penicillins is possible in hospitals with a high level of sensitivity to these causative agents of hospital uroinfections. In severe sepsis and septic shock, broad-spectrum drugs and drugs having the highest antimicrobial activity against potential pathogens are preferable (carbapenems).

Table 6 presents recommendations for empiric antibiotic therapy in patients depending on the clinical form of sepsis.

The most common multidrug-resistant causative agents of uroinfections are enterobacteria and *P. aeruginosa*. Among enterobacteria, *E. coli* is highly resistant to almost all of the most commonly prescribed antibacterial drugs in urological practice, with the exception of carbapenems. After identification of the pathogen, in the presence of positive changes in the patient's condition, de-escalation is recommended (crossover to a drug of a narrower spectrum, as a rule, in monotherapy). In most clinical situations, with adequate surgical debridement of the focus, a 7–10-day course of antibiotic therapy is sufficient [23]. Discharge within 10 days is justified in sepsis caused by *P. aeruginosa* or *Acineto-*

Table 5 / Таблица 5

Antibacterial parenteral therapy of urosepsis, clinical recommendations EAU [20]
Антибактериальная парентеральная терапия уросепсиса, клинические рекомендации Европейской ассоциации урологов [20]

Antibiotic	Daily dose	Comments
Cefotaxime	2 g three times a day	7–10 days Longer courses are indicated for slow clinical response
Ceftazidime	1–2 g three times a day	
Ceftriaxone	1–2 g one time a day	
Cefepime	2 g two times a day	
Piperacillin/tazobactam	4.5 g three times a day	
Ceftolozane/tazobactam	1.5 g three times a day	
Ceftazidime/avibactam	2.5 g three times a day	
Gentamicin*	5 mg/kg per day	
Amikacin*	15 mg/kg per day	
Ertapenem	1 g one times a day	
Imipenem/cilastatin	0.5 g three times a day	
Meropenem	1 g three times a day	

Note. * Not studied as monotherapy for urosepsis.

Table 6 / Таблица 6

Empirical antibiotic therapy in various clinical forms of sepsis [21, 22]

Эмпирическая антибактериальная терапия при разных клинических формах сепсиса [21, 22]

Clinical form of sepsis	Antibiotic therapy regimen
Community-acquired sepsis	Inhibitor-protected penicillins
piperacillin/tazobactam (amoxicillin/clavulanate, amoxicillin/sulbactam), ceftriaxone, cefoperazone/sulbactam, cefepime/sulbactam, ertapenem, ciprofloxacin, levofloxacin, moxifloxacin	Пиперациллин/тазобактам, эртапенем, ципрофлоксацин, левофлоксацин, моксифлоксацин
Hospital sepsis without risk of discharge of bacteria with multiple antibiotic resistance	Piperacillin/tazobactam, ertapenem, ciprofloxacin, levofloxacin, moxifloxacin
Hospital sepsis with risk of discharge of bacteria with multiple antibiotic resistance	Imipenem, meropenem, doripenem, colistin, ceftazidime/avibactam, ceftolozane/tazobactam ± drugs active against gram-positive microorganisms (vancomycin, daptomycin)
Risk of fungal sepsis or microbiologically proven invasive candidiasis	Fluconazole, voriconazole, caspofungin, micafungin, anidulafungin

bacter spp., as well as in patients with neutropenia or delayed clinical response.

The forms of urosepsis that are most difficult to treat include septic lesions caused by nosocomial infection, which is associated with hospital-acquired infection pathogens that have low sensitivity to antibacterial drugs. Hence, the methods of nosocomial urosepsis prevention are given utmost significance. The most effective methods are as follows [20]:

- isolation of all patients infected with multi-resistant strains of microorganisms to avoid cross-infection;
- rational use of antibiotics for both prophylaxis and treatment of confirmed infections to prevent occurrence of resistant strains. The choice of antimicrobial drugs should be based on data on the causative agents of infections prevalent in the given medical institution;
- reduction of hospitalization. Prolonged hospital stay before surgery can increase the frequency of nosocomial infections;
- removal of the indwelling urethral catheter at the earliest (according to the patient's condition). The development of nosocomial urinary tract infection is facilitated by both bladder catheterization and ureteral stenting;
- the use of a closed drainage system and minimization of damage to the system integrity (for example, for collecting urine samples or the bladder irrigation);
- use of minimally invasive methods to eliminate urinary tract obstruction until the patient's condition is stabilized;
- compliance with common aseptic practices every day, including routine use of disposable gloves, frequent hand hygiene, and adherence to infection control measures to prevent cross-infection.

CONCLUSIONS

Urosepsis treatment is based on the general principles of sepsis treatment, besides considering the elimination of urinary obstruction. Surgical intervention for the "urological" cause of sepsis should be performed no later than 2 hours because effective intensive therapy for sepsis is possible only if urine outflow is restored and the focus of infection is completely lavaged surgically.

Urosepsis can develop in the presence of both community-acquired and nosocomial infections. Nonetheless, most cases of urosepsis of nosocomial etiology can be prevented through measures aimed at preventing the persistence of nosocomial infection, for example, reduction of the patient's hospital stay, early removal of the bladder catheter, reduction of the number of unnecessary catheterizations, rational use of closed drainage systems, and compliance with common rules of daily asepsis to avoid cross-infection.

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