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INFECTIONS AND THEIR CAUSATIVE AGENTS IN INTENSIVE CARE UNITS (LITERATURE REVIEW)

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Abstract. Pathogens of nosocomial infections are formed in hospitals in conditions of close contact between individual patients, as well as between patients and staff, which leads to the exchange of strains of microorganisms. In parallel, the formation of antibiotic-resistant strains occurs against the background of intensive use of antimicrobial drugs. The purpose of the review is to summarize the available modern literature data on the most common infectious pathogens in intensive care units (ICU). The review presents data on the most frequently developing infectious complications in the ICU and their causative agents. Data on the similarities and differences of the microbial spectrum depending on the ICU profile are presented. Conclusion. Nosocomial infection of patients in intensive care units is characterized by complex epidemiological and pathophysiological mechanisms of occurrence and development. An increase in the frequency of release of multidrug-resistant microorganisms complicates the implementation of adequate antibiotic therapy, including initial empirical antibiotic therapy, which significantly increases the role of preventive measures.

Keywords: infections, risk factors, pneumonia, angiogenic infections, antibiotic resistance, intensive care units

ИНФЕКЦИИ И ИХ ВОЗБУДИТЕЛИ В ОТДЕЛЕНИЯХ РЕАНИМАЦИИ И ИНТЕНСИВНОЙ ТЕРАПИИ (ОБЗОР ЛИТЕРАТУРЫ)

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Резюме. Возбудители внутрибольничных инфекций формируются в стационарах в условиях тесного контакта между отдельными пациентами, а также между больными и персоналом, что приводит к обмену штаммами

микроорганизмов. Параллельно на фоне интенсивного применения антимикробных препаратов происходит формирование антибиотикорезистентных штаммов. Цель обзора — обобщить имеющиеся современные литературные данные о наиболее часто встречающихся в отделениях реанимации и интенсивной терапии (ОРИТ) инфекционных возбудителях. В обзоре представлен обзор исследований, посвященных микробному профилю ОРИТ и нозокомиальным инфекциям. Приведены данные о сходствах и различиях микробного спектра в зависимости от профиля ОРИТ. Внутрибольничное инфицирование пациентов отделений реанимации и интенсивной терапии характеризуется сложными эпидемиологическими и патофизиологическими механизмами возникновения и развития. Увеличение частоты выделения микроорганизмов с множественной лекарственной устойчивостью усложняет проведение адекватной антибиотикотерапии, в том числе и стартовой эмпирической антибиотикотерапии, что значительно увеличивает роль проведения профилактических мероприятий.

Ключевые слова: инфекции, факторы риска, пневмония, ангиогенные инфекции, антибиотикорезистентность, отделения интенсивной терапии

INTRODUCTION. CONCEPT OF HOSPITAL STRAINS

Rapid introduction of infection control measures and rules of asepsis and antiseptics in modern hospitals has led to evolution of both pathogenic and opportunistic microorganisms, resulting in the selection of new, so-called hospital strains.

A hospital strain is a microorganism that has changed its genetic properties circulating in the department. As a result of mutations or gene transfer (plasmids), it has acquired some characteristic features that are not peculiar to the "wild" strain, allowing it to survive in hospital conditions. Studies indicate that, as a rule, typical characteristics of a hospital strain include resistance to antimicrobial agents (antibiotics, disinfectants, antiseptics, etc.), increased virulence, resistance in the external environment, the ability to circulate for a long time in hospital conditions, enhanced colonization and adhesive properties, competitive activity and genetic uniformity [8]. Hospital-acquired infections (HAIs) are formed in hospitals in close contact between patients, as well as between patients and staff. Thus, there is an exchange of microorganism strains. Simultaneously, intensive and sometimes excessive use of antimicrobial drugs leads to the selection of antibiotic-resistant strains. As a result, a microecological situation characterized by the dominance of certain strains of microorganisms and the prevalence of antibiotic-resistant strains among them is formed in medical institutions. Microbiological studies show that the "landscape" of HAI pathogens dynamically changes even within one intensive care unit (ICU), which is associated with changes of operation mode in the clinic, contingent of patients, intensity of the treatment process, modes of antibiotic prevention and therapy [1, 3].

The most severe cases of healthcare-associated infections (HCAIs) are connected with hospital strains. The risk of mortality in patients infected with resistant microorganisms is two to three times higher than in patients with strains that are sensitive to antibacterial drugs. As the duration of stay in a hospital lengthens, the likelihood of patient's own microflora being replaced by hospital microflora increases, and consequently, infections caused by hospital microflora develop.

There are endogenous and exogenous sources of healthcare-associated infections which are relevant for ICU patients.

Endogenous sources of HCAIs are: obligate patients' microflora of skin, urogenital system (UGS), gastrointestinal tract (GIT), as well as foci of chronic infection that a patient had prior to hospitalization. Endogenous infection can occur in critically ill patients by translocation of intestinal flora into the bloodstream and then into the area of surgical intervention due to deep tissue hypoxia. Tissues can also be contaminated by normal microflora of organs when their integrity is violated during surgical intervention and migration of microflora from the focus of chronic infection resulting in purulent-septic process in the area of surgical intervention.

Exogenous sources of HCAIs in ICU include hands of medical personnel, invasive devices, medical equipment, air, water and foodstuffs. The spread of infection may be caused by a pathogen itself: there is evidence that *Enterococcus* spp. is more likely to be transmitted by contact through hands of personnel. Sources of *P. aeruginosa* can be ventilators and other equipment, and infection with *S. aureus* and *K. pneumoniae* is more often airborne, through air ducts and staff hands. Hidden carriage of Staphylococcus aureus among medical personnel plays a major role in pathogenesis of HCAI. Literature also contains data pointing to staff cell phones and stethoscopes as sources of nosocomial infection [14].

In general, it is possible to identify a number of factors associated with a high level of nosocomial infection in

intensive care units: stay in ICU for more than 48 hours; a large number of therapeutic and diagnostic manipulations; emergency manipulations during resuscitation; duration of ventilator support; intravascular and urinary catheters, parenteral nutrition; frequency and duration of antimicrobial drugs use; crowdedness of resuscitation beds in wards; number of patients assigned to one medical worker; staff turnover; unfair passing/conducting of periodic medical check-ups; neglect of aseptic and antiseptic rules by the staff when performing therapeutic and diagnostic manipulations; inadequate disinfection and sterilization of medical instruments and equipment; non-compliance with isolation and restriction measures, if necessary; inadequate delimitation of "clean" and "dirty" areas due to insufficient space in the department; insufficient amount of sanitary and technical equipment, consumables and disinfectants; deterioration of medical equipment, non-compliance with operating conditions.

AIM

The aim of the review is to summarize available current literature on the most common infectious agents in intensive care units.

STRUCTURE OF HEALTHCARE-ASSOCIATED INFECTIONS IN INTENSIVE CARE UNITS

According to the EPIC (European Prevalence of Infection in Intensive Care) multicenter survey conducted in 17 European countries (1417 ICUs and 9565 patients participated in the survey), catheter-related bloodstream infections (CRBSIs) are among the top three leading ICU-associated infections, along with catheter-associated urinary tract infection and ventilator-associated pneumonia (VAP).

Angiogenic infections, or catheter-related bloodstream infections, are the third most common among all UTIs and the first among the causes of primary bacteremia (up to 87%). The number of CRBSIs varies in different departments and hospitals by structure and profile and, according to various studies, ranges from 2.9 cases per 1000 days of catheterization in specialized ICUs and up to 7.7 cases in general ICU patients [39]. Risks of CRBSIs increase in direct proportion to the duration of catheterization — at catheterization periods up to 7 days, the development of infection is observed in 5% of patients, and in 36% of patients if catheterization lasts for more than 1 month. The association of sepsis with an infected catheter, according to different data, ranges from 20 to 55% [44].

The greatest etiologic role in the development of CRBSIs belongs to *coagulase-negative staphylococci* (34–49.1%) and *S. aureus* (11.9–17%). Infections caused by *Enterococcus* spp. (5.9–6%), *Candida* spp. (7.2–9%) and *Pseudomonas* spp. (4.9-6%) are less common [7].

Two types of infection are possible in CRBSIs. The first is extraluminal, when normal microflora of patient's skin enters a bloodstream along an outer surface of a catheter. This type of infection is typical (up to 60% of cases) for short-term catheters and develops, as a rule, within the first 10 days. If catheterization is prolonged and asepsis is violated during catheter use or infusion solution preparation, intraluminal infection is possible.

There are certain etiologic differences for extra- and intraluminal CRBSIs. Extraluminal infections are more often caused by *coagulase-negative staphylococci, S. epidermidis, S. aureus, Corynebacterium* spp., and *Bacillus* spp. Extraluminal infection with *P. aeruginosa, Acinetobacter* spp. and *Candida albicans* is also possible in case it is brought from the skin of medical personnel's hands. Intraluminal CRBSIs are more often caused by *Enterobacter* spp. and *Citrobacter* spp. [21, 29].

Ventilator-associated pneumonia (VAP) is a specific for intensive care units, which is an inflammatory lung lesion that develops not earlier than 48 h from the moment of intubation and initiation of ventilatory support in the absence of signs of pulmonary infection when ventilator support is initiated [15]. During the first two days of ventilatory support the risk of VAP is low (0.5%), after 72 h — already 50%, and by 8–10 days — 80%. Each subsequent day of ventilator over the third day increases the number of cases by 1–4%.

VAP is the most common CRBSI in ICU — it accounts for up to 86% of all cases of nosocomial pneumonia in surgical ICU patients. According to a number of studies, the average incidence of VAP reaches 27% of all cases of prolonged ventilation and remains practically unchanged over the last 20 years [33, 45].

VAP can develop due to exogenous or endogenous infection. Exogenous sources of infection include endotracheal tubes, tracheostomy cannulas, breathing circuits, valves and humidifiers of ventilators, inhalers, catheters used for sanitation, and contaminated air. Endogenous infection occurs via patient's own microflora — skin, nasopharynx, oropharynx, sinuses, esophagus, stomach and intestines, urinary tract and foci of chronic infection.

The most important risk factors for the development of VAP are: prolonged ventilation (more than 72 h), the severity of a patient's condition, repeated surgical interventions, inadequacy of previous antibiotic therapy, abdominal sepsis, chronic lung diseases, emergency

surgery, unconsciousness of the patient, aspiration and emergency intubation.

The incidence and nature of VAP caused by a particular pathogen depends on the microbiologic landscape of a particular ward. Microbial spectrum of possible pathogens includes Gram-positive (*S. aureus* — 15–35%, *S. pneumoniae* — 10–20%) and Gram-negative flora (*P. aeruginosa, Enterobacteriacae* spp., *A. baumanii, H. influenzae, E. coli, K. pneumoniae*), to which a leading etiologic role belongs. 17–40% of VAP are polymicrobial [25].

Early and late forms of VAP are usually distinguished according to terms of VAP development. Early VAP develops during the first 5 days of hospitalization and is associated with antimicrobial-sensitive pathogens and favorable prognosis. Late VAP does not develop before the 6th day of hospitalization and is associated with a high risk of multidrug-resistant pathogens [18].

Catheter-associated urinary tract infections (UTIs). According to the Russian multicenter ERGINI study (2013), urinary tract infections rank second in the structure of nosocomial infections with a frequency of 16.7%. According to the EPIC II study (Vincent J.-L., 2009), UTIs account for 19.7% of all cases of CRBSI in ICUs of Eastern Europe. It was found that 79–97% of UTIs in ICU are associated with urethral catheter placement [38, 41].

Urinary tract infections may be the cause of secondary bacteremia or sepsis, risk factors for which include male gender, immunosuppression, neutropenia, renal disease, and malignancy. It has also been found that bacteremia is significantly more frequent in nosocomial urinary infection caused by enterococci and fungi of the genus *Candida.*

Urogenital pathogenic microorganisms causing urinary tract infections in ORIT include gram-negative bacteria of the *Enterobacteriaceae* family (primarily *E. coli, K. pneumoniae, Proteus* spp.), *A. baumanii*, and *P. aeruginosa*; the group of Gram-positive bacteria is represented by *E. faecalis, E. faecium, Staphylococcus aureus* and coagulase-negative staphylococci; fungi of the genus *Candida* have a definite etiologic role in the development of urinary tract infections. Anaerobic and atypical microorganisms are not etiologically significant [16, 22].

ETIOLOGY OF HEALTHCARE-ASSOCIATED INFECTIONS

The most clinically significant and common causative agents of all types of HCAIs in ICU are a limited group of microorganisms called ESKAPE — *Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa*, representatives of the order *Enterobacteriales*.

This statement is true both for the entire structure of nosocomial infections and for infections registered in intensive care units in particular [11]. According to the data for 2020, the share of *Enterobacteriaceae* in the etiology of HCAIs is 53.2%, the most frequent species are *K. pneumoniae* (26.7%) and *E. coli* (14.6%), the share of infection with *P. aeruginosa* and *A. baumannii* was 21.9 and 16.7% of all bacterial pathogens, respectively, *S. aureus* — 7.7% [3, 5].

Hospital biovars produced by HCAI pathogens may include: *Enterobacteriaceae (K. pneumoniae, E. cloacae, E. coli)* producing extended-spectrum β-lactamases (ESBL) or carbapenemases; *Pseudomonas aeruginosa* which are resistant to carbapenems and/or ceftazidime and/or ciprofloxacin; *Acinetobacter* spp. resistant to carbapenems; *Staphylococcus aureus, Staphylococcus epidermidis* resistant to methicillin (MRSA — methicillin-resistant strain of *S. aureus*) and/or vancomycin and/or ciprofloxacin and/or β-lactamase-producing; Vancomycin resistant *Enterococcus* spp. (VRE) — the main role belongs to *E. faecalis* and *E. faecium; Streptococcus pneumoniae* resistant to β-lactam antibiotics; *Candida* spp. resistant to fluconazole [20, 23, 26, 32].

In recent years, Enterobacteriaceae have been the most frequent causative agents of HCAIs in Russian hospitals. Microorganisms of this order demonstrate high levels of resistance to antimicrobials, with resistance to cephalosporins and carbapenems being of the greatest clinical significance. Resistance of hospital-acquired *Enterobacteriaceae* to cephalosporins reaches >80%, mainly due to the spread of ESBL-producing strains [38]. According to 2020 data, the resistance of *K. pneumoniae* and *E. coli* to ceftazidime amounted to 85.3% and 45.1%, respectively. There is also an increase in resistance to carbapenems, including those mediated by carbapenemase production by hospital strains of *Enterobacteriaceae.* By 2020, 50.4 and 68.7% of *K. pneumoniae* strains and 4.7 and 5.8% of *E. coli* strains, were resistant to meropenem and ertapenem respectively [19, 23].

In addition to antibiotic resistance of hospitalized strains, increasing resistance of out-of-hospital strains of *Enterobacteriaceae* is also a problem. According to the 2018-2019 data, *E. coli* out-of-hospital isolates were resistant to amoxicillin/clavulanate (41.4%) and ciprofloxacin (37.2%), as well as to cefotaxime (32.2%), cefepime (19.7%) and ceftolozane/tazobactam (3.8%) mainly due to the production of ESBL [19].

Pseudomonas aeruginosa is the second or third most frequent species after *Klebsiella pneumoniae,* followed by *Acinetobacter* spp. in some hospitals. Genes of acquired carbapenemases were detected in 42.4% of hospital-acquired isolates of this microorganism, including: metallo-

β-lactamases (MBL) of VIM and IMP groups — 83.2 and 0.8%, respectively; serine carbapenemases of GES-5 group — 15.2%; both MBL and serine carbapenemases were produced simultaneously by 0.8% of isolates. MBL producers were characterized by resistance to all antimicrobials except aztreonam and polymyxins; GES-5 producers were resistant to most drugs except ceftazidime/avibactam and polymyxins [23]. *Pseudomonas aeruginosa* showed the greatest resistance to meropenem — 52.5%, cefepime — 52.8%, ceftazidime — 55.0%, imipenem — 57.9%, piperacillin/tazobactam — 61.1%, ciprofloxacin — 63.2%. In 2020, *Acinetobacter* spp. (mainly Acinetobacter baumannii) was the fourth most frequent species (14.3%) after *K. pneumoniae* (26.7%), *P. aeruginosa* (16.5%) and *E. coli* (14.6%). *A. baumannii* and related species have significantly lower natural sensitivity to most β-lactam antibiotics, including penicillins and cephalosporins, which limits the choice of drugs with potential applicability for therapy of infections caused by *Acinetobacter* spp. [23]. 90.5% of *A. baumannii* isolates were found to have genes for acquired carbapenemases, mostly belonging to molecular class D (98.6%), which mediates resistance to imipenem and meropenem. The vast majority of isolates were also resistant to ciprofloxacin (98.1%), amikacin (91.8%) and gentamicin (82.7%). The frequency of resistance to tobramycin and trimetho-prim/sulfamethoxazole was 64.5 and 52.8%, respectively.

The proportion of HCAIs caused by *Staphylococcus aureus* is 7.7%. In comparison with the earlier period of observation, this can be characterized as a decrease. The main problem of *S. aureus* resistance is resistance to β-lactam antibiotics acquired through the production of β-lactamases. According to multicenter Russian studies, MRSA accounted for 24.9 to 66.9% of all infections caused by *S. aureus*. The most effective antibiotics against this pathogen are glycopeptides and lipopeptides (vancomycin, telavancin, daptomycin), oxazolidinones (linezolid, tedizolid), anti-MRSA cephalosporins (ceftaroline) and glycylcyclines (tigecycline). All studied strains were sensitive to these antimicrobials [19].

According to the guidelines "Diagnosis and antimicrobial therapy of infections caused by multidrug-resistant strains of microorganisms", issued by the Association of Anesthesiologists and Resuscitators, there are specific risk factors for the development of multidrug-resistant infections [8].

Risk factors for infections caused by Enterobacteriaceae — ELBS producers are: hospitalization during prior 3 months or current hospitalization; intake of antibiotics (III–IV generation cephalosporins, fluoroquinolones) for any reason during previous 3 months; staying in long-term care facilities (nursing home, orphanage, hospice); hemodialysis; comorbidity: Diabetes mellitus, liver cirrhosis, chronic kidney disease (CKD) [17, 27, 35, 43].

Risk factors for infections caused by MRSA: known high prevalence of MRSA in the ward where the patient is located; previous (within 3 months) hospitalization with surgical interventions and invasive procedures (especially implantation of artificial materials and/or devices); taking broad-spectrum antibiotics (fluoroquinolones, to a lesser extent III–IV generation cephalosporins) for any reason within the previous 3 months; presence of an intravascular catheter; nasal carriage of MRSA; intravenous drug abuse; presence of trophic ulcers or pressure sores [17, 30, 36, 37].

Risk factors for infections caused by multidrug-resistant P. aeruginosa are: prior therapy with cephalosporins, fluoroquinolones, and carbapenems; prolonged stay in ICU; ventilatory support >4 days; sternotomy; presence of bronchiectasis, cystic fibrosis; and presence of urethral catheter [17, 28, 31, 34].

Risk factors for infections caused by carbapenem-resistant Enterobacteriaceae are: known high prevalence of carbapenem-resistant Enterobacteriaceae in a certain department; previous carbapenem therapy; colonization of the patient's gut by carbapenem-resistant Enterobacteriaceae [17, 40, 42].

Assessment of these factors is necessary when empirical antimicrobial therapy is initiated, since the choice of the optimal antimicrobial agent is directly related to probable infection of a patient with multidrug-resistant strains [6].

REVIEW OF MICROBIAL LANDSCAPE STUDIES IN INTENSIVE CARE UNITS OF DIFFERENT PROFILES

The share of each pathogen in the structure of HCAIs in ICUs is determined by the nature of the most frequent forms of HCAIs, the profile of a hospital and a particular ICU. Each medical institution is characterized by its own microbial landscape: in surgical hospitals, *S. aureus et epidermidis, Streptococcus* spp., *P. aeruginosa, Enterobacter* spp. are more likely to cause HCAIs; *P. aeruginosa and* S. *aureus* play a major etiological role in burn centers; herpes viruses, cytomegaloviruses, *Candida fungi* and pneumocysts are particularly dangerous in wards for haematology and HIV-infected patients due to their immunosuppression [10].

Literature data also demonstrate differences in etiological structure of HCAIs in intensive care units of different profiles.

According to a survey on the HCAIs etiology in neurosurgical ICUs conducted in 2017, Gram-positive flora was responsible for 46.75% of HCAIs, Gram-negative flora — for 48.05%, and fungi — for 5.19% of cases.

The most frequently isolated Gram-negative pathogens were *K. pneumoniae* (14.29%), *A. baumannii* (15.58%), *P. aeruginosa* (11.69%), and among Gram-positive patho-

gens — *S. aureus, E. faecalis* and *S. epidermidis*; the total share of these six microorganisms accounted for 80.51% of all reported HCAIs during the observation period. The *Enterococcus spp.* bacteria isolated were mainly represented by *E. faecalis* (6.49%) and *E. faecium* [24].

A 2019 survey compares microbial landscapes of neurological and surgical ICUs. *Pseudomonas aeruginosa* and *Proteus* spp. were most frequently isolated in neurological ICUs — 25.3% of cases for each strain. The proportion of *Enterobacter spp.* was 16.3%, *Staphylococcus* spp. — 10%, *E. coli* — 7.7%, *Streptococcus* spp. — 5,4%. In total, Gram-negative flora caused HCAIs in neurological ICUs in 84.6% of cases. The most frequent flora isolated from surgical ICU patients and environmental objects were *Pseudomonas aeruginosa* — 21.7%, *Enterobacter* spp. — 16.5%, *Staphylococcus* spp. — 15.2% and *Proteus vulgaris* — 14.83%. The proportion of gram-negative microorganisms was 78.3%.

Thus, a surgical ICU profile was associated with a higher proportion of cefoperazone-resistant Gram-positive flora (*Staphylococcus* spp., *Streptococcus* spp.).

In 2020–2021 there were performed a survey studying etiological structures of HCAIs in surgical and therapeutic ICUs,. However, the association between an increased proportion of Gram-positive pathogens in surgical ICUs was not confirmed. In both observation years, the proportion of Gram-positive flora was higher in the therapeutic ICU — 39.4 and 31.5% versus 34.7 and 21.2% in the surgical ICU, respectively. The dominant pathogens were representatives of 4 families: *Moraxellaceae* (15.6–33.3%), *Enterobacteriaceae* (26.8–32.6%), *Staphylococcaceae* (17.7–23.5%), *Pseudomonadaceae* (4.9–11.9%). A significantly lower proportion of infections caused by *Pseudomonas aeruginosa* (up to 11.9%) draws attention in comparison with the previous survey [2].

Analysis of the microbial landscapes of general intensive care units in two multidisciplinary hospitals also demonstrates significant differences in Gram-positive flora prevalence. A research performed in Omsk town in 2011 testifies to the equal role of Gram-negative and Gram-positive microbiota in the etiology of HCAIs. However, a similar study in Tula town in 2014 revealed the predominance of Gram-negative flora in the structure of HCAIs (75% of cases). The leading etiological role also belonged to different microorganisms: in the first study, *Klebsiella spp.* (46%), *E. coli* (22%) and *Enterobacter* spp. (17%) caused the largest number of cases, while in the second study — *P. aeruginosa* (50%) and equal proportions of *E. coli* and *S. epidermidis* — 17% of cases each [9, 12].

CONCLUSION

Nosocomial infection in ICU patients is characterized by complex epidemiological and pathophysiological mechanisms of emergence and development. The increasing frequency of multidrug-resistant microorganisms complicates the adequate antibiotic therapy of HCAIs, including the initial empirical antibiotic therapy, which significantly increases the role of preventive measures. The analysis of microbiological monitoring data from different intensive care units revealed significant differences in both the species structure and sensitivity to antimicrobials of isolated microorganisms. There were no specific microbial landscape features which would be specific to certain ICU profiles. Thus, it is necessary to develop internal protocols for empirical antimicrobial therapy and perioperative antibiotic prevention individually for each ward/hospital. Therefore, regular analysis of the microbial landscape and drug susceptibility profiles of detected microorganisms is important. It should be noted that an individual and comprehensive approach to ICU nosocomial infection is needed. This approach, which should take into account local characteristics of the microflora species composition, can provide a reliable reduction in overall and attributable mortality, as well as reduce the length of stay of patients in these departments.

ADDITIONAL INFORMATION

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Декларация о наличии данных. Условие доступа к данным неприменимо — новые данные не генерируются.

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