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Review article

PROSPECTS FOR USE OF CEFTOLOSAN-TAZOBACTAM IN PROVIDING MEDICAL CARE TO VICTIMS IN A THIRD-LEVEL HOSPITAL AND DURING INTER-HOSPITAL MEDICAL EVACUATION

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Abstract. It is noted that nosocomial infections are a serious threat to the safety of hospital patients due to their high prevalence and high mortality rate. The prospects of using a new antibacterial drug ceftolosan-tazobactam as a starting empirical therapy in patients with a high risk of nosocomial infection caused by multidrug-resistant microorganisms in a level III hospital and during inter-hospital medical evacuation are considered.

Key words: *antibiotic resistance, ceftolosan, empirical antibacterial therapy, inter-hospital medical evacuation, level III hospital, nosocomial infection, tazobactam, zerbaxa*

Conflict of interest. The authors declare no conflict of interest

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Обзорная статья

ПЕРСПЕКТИВЫ ПРИМЕНЕНИЯ ЦЕФТОЛОЗАНА-ТАЗОБАКТАМА ПРИ ОКАЗАНИИ МЕДИЦИНСКОЙ ПОМОЩИ ПАЦИЕНТАМ В ЛЕЧЕБНОЙ МЕДИЦИНСКОЙ ОРГАНИЗАЦИИ ТРЕТЬЕГО УРОВНЯ И ВО ВРЕМЯ ПРОВЕДЕНИЯ МЕЖБОЛЬНИЧНОЙ МЕДИЦИНСКОЙ ЭВАКУАЦИИ

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Резюме. Отмечено, что нозокомиальные инфекции являются серьезной угрозой безопасности пациентов стационаров в силу своей высокой распространенности и высокого уровня летальности. Рассмотрены перспективы применения нового антибактериального препарата цефтолозан-тазобактам в качестве стартовой эмпирической терапии у пациентов с высоким риском развития нозокомиальной инфекции, вызванной микроорганизмами с множественной лекарственной устойчивостью, в лечебной медицинской организации (ЛМО) 3-го уровня и во время проведения межбольничной медицинской эвакуации.

Ключевые слова: *антибиотикорезистентность, зербакса,* лечебная медицинская организация *3-го уровня, межбольничная медицинская эвакуация, нозокомиальная инфекция, тазобактам, цефтолозан, эмпирическая антибактериальная терапия*

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Infectious complications are a considerable threat to the safety of hospital pa-tients due to their high prevalence and high mortality rate.

The development of infectious complications in patients with polytrauma is virtually a natural stage with occurence of 1,5% in light injuries and of up to 90% – in severe injuries, which makes at least 50% of the total number of those hospitalized with injuries [1]. In the 3rd period of traumatic illness – on the 3rd through the 10th day – the incidence of infectious complications ex-ceeds 80% [2]. In burn patients who survived the period of burnshock, infec-tious complications are the leading cause of mortality in 85-100% of cases, starting from the 3-rd day [3].

It is also characteristic that hospital microflora is found in 85-100% of cases of infectious complications of polytrauma [4, 5].

The nosocomial infections caused by multidrug-resistant and pan-resistant bacterial strains are the most problematic. Multidrug-resistant (MDR) patho-gens – that are resistant to three or more classes of antibiotics; extensively drug resistant (XDR) – that are resistant to all but one or two classes of anti-biotics; panresistant pathogens (PDR) – that are resistant to all known drug classes. Gram-negative bacteria resistance to carbapenems, with the excep-tion of strains with natural resistance to these drugs, is a marker of XDR or PDR [6].

According to the Russian "SKAT" program clinical guidelines, the highest prevalence of nosocomial infections was observed in intensive care units (ICU) – 26.28%. Compared with nosocomial infections are more severe than diseases provoked by community-acquired pathogens. In nosocomial infec-tion, the development of severe sepsis with multiple organ failure (43.8%) and of septic shock (12.5%) is observed significantly more often compared with community-acquired infections – 16.3 and 2.9%, respectively [7].

Patients in the ICU are especially susceptible to infection due to severity of their condition, to decrease in protective immune mechanisms, to background diseases (diabetes mellitus, malignant neoplasms, etc.), to a large number of invasive procedures, including the administration of medications and injec-tions, to presence of persistent potential ports of infection – drains, catheters, electrodes [8].

On the other hand, if there are a high workload and a lack of staff, ICU per-sonnel can pay not enough attention to taking measures to prevent the spread of nosocomial infection, in particular, to hand hygiene. This can result in the cross-contamination of patients with hospital microorganisms [9].

One of the major ICU challenges is an overload, which results in overcrowd-ing of patients and in a high workload, and significantly reduces the effective-ness of measures to prevent contamination and cross-contamination of pa-tients with MDR and XDR microorganisms.

In Russian hospitals, among nosocomial bacterial infections, infections of the lower respiratory tract prevail – such as pneumonia and tracheo-bronchitis (42%). The share of them significantly exceeds the share of infections of oth-er localizations – such as urinary tract (19%), skin and soft tissues (13.4%), abdominal infections (11.4%) and bloodstream infections (4.8%) [7].

Pneumonia is called nosocomial, if it occurs 48 hours after hospitalization. In ICU patients, at least half of nosocomial pneumonias (NP) are ventilator-associated pneumonias (VAP). Early – up to 4 days – nosocomial pneumoni-as are predominantly induced by sensitive microorganisms, while late noso-comial pneumonias –NP and VAP – are more often provoked by MDR and XDR pathogens.

Despite numerous studies that resulted in the introduction of set of measures for the prevention of VAP, VAP remains a major nosocomial infection in the ICU with an incidence rate of 9–27% [10]. Early studies showed that the VAP mortality rate is 33-50%, but this number varies significantly depending on the course of an underlying disease and on the severity of the patient's condition.

According to the modern epidemiological data, nosocomial urinary tract infec-tions (UTIs) rank second after lower respiratory tract infections with the inci-dence of 16.7%, [11]. In most cases, they are caused by multidrug-resistant pathogens and require longer courses of antibiotic therapy in comparison with uncomplicated infections. Despite the fact that nosocomial infections of the urinary tract less affect the prognosis and less increase the risk of patient's death in a hospital in comparison with respiratory tract infections and with complicated abdominal infections, it should be kept

in mind that in 15 - 25 % of cases, they are accompanied by bacteriaemia, which leads to an increase in attributive mortality by 4–30% [12,13].

Patients with complicated intra-abdominal infection (cIAI) represent a signifi-cant number of all patients in a multi-speciality hospital. cIAI is an important reason of hospitalization to intensive care units and is the second most com-mon cause of death in ICU patients. In some subgroups of patients, the mor-tality rate from cIAI exceeds 30% [14].

Complicated IAIs are characterized by a solution of continuity of the gastroin-testinal tract (GIT) – through perforation of the organ wall or through its ne-crosis – followed by bacterial contamination of the abdominal cavity and / or of the retroperitoneal space with the further development of abscess or peri-tonitis. Successful treatment of cIAI requires not only a timely surgical inter-vention, but also a timely and effective antibacterial therapy [15].

Due to the diversity of gastrointestinal tract normal microflora, cIAIs are often polymicrobial with a predominance of gram-negative facultative anaerobes, mainly of representatives of Enterobacterales order. It is also necessary to remember about gram-positive round bacteria, in particular, Streptococcus spp., Enterococcus spp. and anaerobic microorganisms [14].

In ICUs of modern hospitals, an overwhelming majority of nosocomial infec-tions are associated with bacteria of so-called ESKAPE group (Enterococcus spp., Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter bau-mannii, Pseudomonas aeruginosa and Enterobacter spp.), among which there is the largest number of antibacterial drug-resistant strains[16].

The study of the clinical significance of resistance shows

that the highest le-thality and the highest cost of treatment are associated with microorganisms from the ESKAPE group [17].

ESKAPE bacteria are included in the World Health Organization (WHO) list of 12 microorganisms, the fight against which requires urgent development of effective chemotherapy. Carbapenem-resistant gram-negative microorgan-isms: A.baumannii., P. aeruginosa, K.pneumoniae and Enterobacter spp. are included in the category of pathogens of "critical importance"; gram-positive vancomycin-resistant Enterococcus spp. and S.aureus are marked as "high priority" [18].

Moreover, according to the EPIC II study, 62% of ICU infections are caused by gram-negative pathogens. The most common gram-negative pathogens educed from ICU patients are Pseudomonas spp. and Klebsiella spp., as well as Escherichia coli [19].

The mechanisms of multiple resistance observed in pathogens of the ESKAPE group are divided into three main categories: destruction or inactiva-tion of the drug; modification of drug-susceptible target structures; change in permeability or other mechanisms leading to a change in the concentration of the drug in the microbial cell, as well as the formation of biofilms. The genes for resistance factors can be present in bacterial chromosomes, plasmids and transposons [20].

Inactivation of the drug: many bacteria are capable of producing enzymes that irreversibly modify and inactivate antibiotics. These are, for example, be-ta-lactamases, aminoglycoside-modifying enzymes and chloramphenicol acetyltransferases. Beta-lactamases are among the most widespread and well-studied resistance factors. They hydrolyze the beta-lactam ring, which is the basis of all beta-lactam antibiotics, thus, all penicillins, cephalosporins, monobactams, and carbapenems are a potential substrate for beta-lactamases [21].

The classification of beta-lactamases based on molecular structure – the Am-bler scheme – includes the most clinically significant types of beta-lactamases produced by gram-negative bacteria.

Class A includes penicillinases, cephalosporinases, broad-spectrum beta-lactamases, extended-spectrum beta-lactamases (ESBLs), and car-bapenemases. Representatives of class A can inactivate: penicillins (except for temocillin), axiiminocephalosporins of the third generation (ceftazidime, cefotaxime, ceftriaxone), aztreones, cefoperazone, cefamycins and car-bapenems. On the other hand, class A enzymes are sensitive to the action of beta-lactamase inhibitors such as clavulanic acid, sulbactam and tazobactam [22].

Class A includes a number of clinically important enzymes, including ESBL types TEM, SHV and CTX-M and KPC carbapenemases. TEM (from Temo-niera, first educed in 1965 from E. coli) – are widespread not only among en-terobacteria, including K. pneumoniae, Enterobacter spp., but also among non-fermenting microorganisms (P. aeruginosa). Currently, they are most commonly found in E. coli.

Among sulfhydryl-variable (SHV) beta-lactamases, SHV-1, which is the most characteristic of K.pneumoniae, has the greatest clinical significance. The genes encoding beta-lactamases of TEM and SHV subtypes have a high mu-tation frequency, which results in a high variability of the enzymes encoded by them, expanding the spectrum of antibiotic resistance.

Beta-lactamases of the CTX-M subtype were educed from bacteria belonging to the ESKAPE group, which includes K.pneumoniae, A.baumannii, P.aeruginosa, and Enterobacter spp. They got the greatest prevalence and clinical significance in K. pneumoniae isolates.

Group A carbapenemases, in particular KPC-1, are also characteristic of K. pneumoniae isolates. They cause resistance to imipenem, meropene, amoxi-cillin, piperacillin, ceftazidime, aztreonam and ceftriaxone.

Beta-lactamases of class B are represented by metallo-beta-lactamases (MBL), which include Zn2 + as a cofactor. MBL producing bacteria are re-sistant to all beta-lactams (penicillins, cephalosporins, carbapenems), with the exception of aztreonam, as well as to beta-lactamase inhibitors. The genes encoding MBL production are located on plasmids, so they can be easily transferred to other microorganisms. This is the most important mech-anism for the emergence of MDR and XDR strains within cross-contamination. The most widespread MBL-IMP (imipenemase), VIM (Verona integron encoded metallo-β-lactamases), NDM-1 (New Delhi metallo-beta-lactamase-1) are characteristic of P. aeruginosa, K. pneumoniae, A .baumannii and Enterobacter cloacae isolates[20].

Modification of drug-binding loci. Some resistant microorganisms avoid inter-action with antimicrobial drugs by modifying the target loci. Mutation of the gene encoding penicillin-binding protein (PBP) results in the expression of unique penicillin-binding proteins. For example, PBP2 is a protein unique to S. aureus that has low affinity for all beta-lactams and is the predominant type of PBP in methicillin-resistant S. aureus, replacing other PBPs and allowing bacteria to remain viable in the presence of many beta-lactam antibiotics, in-cluding methicillin. Similarly, by modifying amino acid sequences, E. faecium and E. faecalis can increase their resistance to vancomycin and teicoplanin glycopeptides [22, 23].

Decrease in intracellular drug concentration. The antibiotics concentration in-side bacterial cells is determined by the balance between its absorption and its elimination. A decrease in intracellular concentration is one of the mechanisms of resistance to antibiotic action. This can be achieved by reducing the number of protein channels on the outer membrane of the bacterium, which reduces the uptake of the antibiotic, as well as by the presence of efflux pumps, which reduce its intracellular concentration. Many efflux pumps, being one of the mechanisms for the formation of multiresistance, are active against various antibiotics. P. aeruginosa and A. baumannii, for which both mecha-nisms are characteristic, can serve as a spectacular example. The loss of porin proteins, which form the channels for hydrophilic substances in the cell membrane, allows the bacterial cell to reduce the level of carbapenems' pen-etration through it. While the accumulation of high concentrations of antibiot-

ics inside the cell is prevented by the presence of certain types of efflux pumps that are active against fluoroquinolones, beta-lactams, tetracyclines, including tigecycline, macrolides and aminoglycosides [24].

Biofilm formation. Biofilms are polymicrobial associations that form on biologi-cal or nonbiological surfaces. They are united by a matrix of extracellular bi-opolymers produced by microorganisms inhabiting biofilms. Inside the biofilm, conditions that are favorable for existence of microorganisms and that oppose the effective action of antimicrobial drugs are created. The formation of bio-films which provide mechanical and biochemical protection of microorganisms is a powerful factor of resistance in vivo. In hospital conditions, the most common inhabitants of biofilms are S. aureus, P. aeruginosa, A. baumannii, and K pneumoniae [25].

A widespread occurrence of resistant flora, in particular, of producers of ex-tended spectrum beta-lactamases resulted in a widespread use of car-bapenems for treatment of nosocomial infections. Undergoing, actually, di-rected evolutionary selection, the number of Enterobacterales strains resistant to carbapenems grows annually – mainly through acquisition of re-sistance by production of plasmid-mediated carbapenemases. Thus, a "vi-cious circle" is formed, in which the effectiveness of carbapenems is progres-sively reduced. That results in an inevitable increase in the number of cases of ineffective treatment, in the growth of antibiotic resistance and urges the need for use of new drugs [26].

The development of new combinations of cephalosporins and beta-lactamase inhibitors is an attempt to introduce "carbapenem-saving technologies" – a set of measures designed to rationalize first the empirical antibacterial thera-py, then to reduce the frequency of carbapenem use as a first-line drug, thereby reducing the rate of selection of carbapenem-resistant microorgan-isms among hospital strains [27].

Ceftolosan - Tazobactam. Ceftolosan is a new broad-spectrum cephalosporin with pronounced antipseudomonal activity, affecting the strains which are highly resistant to other beta-lactams, fluoroquinolones and aminoglycosides, as well as the strains with multiple drug resistance [28].

Ceftolosan is characterized by: multiple mechanisms responsible for P. aeru-ginosa resistance, including AmpC hyperexpression, stability; no cross-resistance with other antipseudomonal drugs and low ability to induce re-sistance in this microorganism [29].

Ceftolosan is also active against enterobacteria, but its activity is counteract-ed by the production of extended-spectrum beta-lactamases and car-bapenemases. The presence of tazobactam, a well-known beta-lactamase inhibitor, broadens the coverage of ceftolosan, through embracing many mi-croorganisms that produce extended spectrum beta-lactamases, as well as anaerobic microorganisms such as Bakteroides spp. [30].

Ceftolosan / tazobactam successfully penetrates the fluid of the epithelial lin-ing of lungs. The concentration of ceftolosan and tazobactam in plasma and pulmonary epithelium grows rapidly, reaching its maximum level by the end of administration. The ratio of the concentration of ceftolosan in the endothelial fluid of the lungs to the plasma concentration in healthy adults was 0.48 [31]. While, in critically ill patients on artificial lung ventilation (ALV), the maximum concentration in the lungs was achieved only up to 4 hours after starting the administration. The concentration ratio in the endothelial fluid of lungs to the plasma concentration was 0.97 (97%) – for ceftolosan and 1.2 (120%) – for tazobactam [32, 33].

Since 2019, nosocomial, including ventilator-associated, pneumonia is an in-dication for the medical use of ceftolosan-tazobactam in the Russian Federa-tion [34].

Interhospital evacuation. The effectiveness of initial empirical antibiotic thera-py is of critical importance for patients with severe infectious complications, sepsis, and septic shock [35]. Early administration of effective antibiotic ther-apy is associated with reduced mortality.

When choosing empirical antibacterial therapy, one should consider: known or the most probable source of infection as well as the most probable patho-gen; local microbiological control data, including the spectrum of sensitivity, the presence of MDR / XDR strains and the most common mechanisms of resistance.

Despite the fact that, according to the definition, nosocomial infections are those that occur 48 hours after the start of inpatient treatment, the contamina-tion of the patient with hospital microorganisms occurs much earlier, some-times even during the first hours of stay in the hospital [8].

This fact acquires an important meaning when a patient is transported from hospital to hospital.

These cases are typical for the everyday practice of doctors of the Disaster Medicine Service (SMK), which are involved in the inter-hospital evacuation of seriously ill patients and patients injured in emergencies (ES). Then the ini-tial volume of care is provided in primary and secondary care hospitals, locat-ed in the immediate vicinity of the event site. For the provision of specialized, including high-tech, medical assistance, renal replacement therapy (RRT), extra-corporal membrane oxygenation (ECMO), patients are transferred to the tertiary care hospitals. As a rule, in such cases medical evacuation is car-ried out between intensive care units. Thus, it should be kept in mind that the transfer of hospital flora between hospitals occurs even in cases when the pa-tient stayed in the ICU of the primary hospital for less than 48 hours. The transfer of hospital strains with different mechanisms of resistance between intensive care units of different hospitals potentially contributes to the for-mation of nosocomial infections pathogens with resistance to all available an-tibacterial drugs, which they effectuate through various mechanisms. Cases of contamination of one patient with several agents of nosocomial infections are not uncommon.

In inter-hospital evacuation, a choice of empirical antibacterial therapy is made, lacking the whole information. Early administration of empiric antibiotic therapy with an antibacterial drug that is most likely to be effective against resistant nosocomial infections is extremely important for successful treatment of patients admitted from other hospitals. The second important prerequisite is an early microbiological testing with the identification of microorganisms and of their spectrum of sensitivity to antibacterial therapy.

In Nikiforov Russian Center of Emergency and Radiation Medicine of EMERCOM of Russia, if a patient arrived from another hospital, a microbiological screening aimed at identifying causative agents of noso-comial infections is routinely performed. In more than 80% of cases (69 out of 85) gram-negative MDRs and XDR- microorganisms were detected. When a patient is admitted to ICU, collection of samples should be performed as early as possible, as it is a key success factor for microbiological diagnostics. Ma-terials for testing should be taken in sufficient volume and from all available loci – nasopharynx, rectum, bronchial washings, blood, replacement of intra-vascular and urethral catheters – all that should be subsequently examined – before (which is particularly inportant) starting empiric antibiotic therapy. A similar approach can also be applied at the stage of inter-hospital evacuation of seriously ill patients and of persons injured in emergencies, specifically when it comes to medical evacuation over long distance, which take several hours or even days.

Given the prevalence of hospital gram-negative flora, the combination of ceftolosan and tazobactam seems to be promising as a starting empiric ther-apy, since it is effective against the most common manifestations of noso-comial infection – cIAI, urinary tract infection (UTI), nosocomial pneumonia, including the cases of sepsis and septic shock [27].

The availability of generic carbapenem medications seems to make the use of protected cephalosporins as components of the first line antibiotic therapy in patients at high risk of MDR / XDR microorganisms economically unattrac-tive. At the same time, pharmacoeconomic analysis showed a high phar-macoeconomic efficiency of using ceftolosan-tazobactam in combination with metronidazole in the treatment of complicated nosocomial intra-abdominal in-fections [36]. In everyday practice, ceftolzan-tazobactam can be used both in monotherapy and in combinations, which promises clinical efficacy of an em-pirical antibiotic therapy regimen.

In our opinion, taking into account the high clinical and pharmacoeconomic efficiency of ceftolosan-tazobactam therapy, its use as monotherapy or in combinations can be considered as an initial empirical treatment in patients with a high risk of gram-negative MDR / XDR infections not only at the stage of inpatient treatment, but also during inter-hospital evacuation.

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