UDC: 616.03 **DOI: 10.18413/2313-8971-2016-2-2-91-98**

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DIABETIC FOOT SYNDROME: IMPORTANCE OF MICROBIOLOGICAL MONITORING AND ANTIMICROBIAL PENETRATION OF CHEMOTHERAPEUTIC AGENTS INTO THE SOFT TISSUE LOWER LIMB IN DETERMINING THE TREATMENT

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Abstract. Foot infections are a common and serious problem in persons with diabetes. Persistent ulcers in patients with diabetic foot syndrome in 85% of cases lead to amputation because of secondary infection and growing gangrene that significantly worsen the prognosis. The review provides the information on the spectrum of microorganisms, initiating the development of clinical and morphological forms of diabetic foot infections. Special attention has been paid to the choice in diabetic foot infections antibacterial medications based on indicators of sensitivity to them by allocated microorganisms and features of therapeutic concentrations formation in the skin, soft tissues or bone. Clinical data of researchers in the degree of penetration of various antibacterial agents in soft tissue and depend on severity lesions. In our review, it was shown that the most common pathogen was Staphylococcus aureus, followed by Pseudomonas aeruginosa, Enterobacteriaceae: E. coli, Proteus spp., Klebsiella pneumoniae, Enterobacter spp., and Acinetobacter spp. due to multidrug-resistant organisms, such as extended-spectrum beta-lactamase-producing Gram-negative rods or methicillin-resistant Staphylococcus aureus have emerged as substantial problem. Data on the frequency and the sensitivity of key pathogens in diabetic foot differ in Russian and foreign researchers, which causes the necessary treatment considering local peculiarities allocated pathogens and the degree of penetration of anti-infective agents in the affected tissues.

Keywords: diabetic foot syndrome, infection, antibiotics, antibiotic resistance, tissue penetration of antibiotic.

Over the past decade, the world number of patients with diabetes mellitus has increased more than 2 times, and reached 387 million people by the end of 2014. According to the prognosis of the International Diabetes Federation, nearly 592 million people will suffer from diabetes by 2035 [1].

Pathogenesis of noninsulin dependent diabetes mellitus is insulin resistance, which is the cause of many metabolic disorders, including hyperglycaemia, hypertriglyceridaemia raising low-density lipoprotein, decrease in high-density lipoprotein, is activated by the process of lipid peroxidation and hyperhomocysteinemia. As a result, of these changes is the development of endothelial dysfunction, which leads to the appearance of neuropathy and angiopathy [2, 3].

One of the late complications of diabetes mellitus is a diabetic foot syndrome, which includes a set of pathological changes on the foot and the lower limbs characterized by the development of diabetic foot ulcer, neuropathic osteoarthropathy, diabetic neuropathy and inflammation or purulence complications in patients with DM. This requires optimization approaches to complex pharmacotherapy [4, 5, 6, 7, 8, 9].

Persistent ulcers in 85% of cases lead to amputation because of secondary infection and

growing gangrene, which dictates the need for epidemiological studies for identification of patients with diabetic foot infections (DFI), determination of both the structure of isolated microorganisms and their sensitivity.

According to Russian authors, predominant species in patients with DFI was Gram-positive cocci – Staphylococcus aureus. Most common gram-negative rods were distinguished nonfermenting gram-negative rods - Pseudomonas aeruginosa and Enterobacteriacae spp.: Escherihia coli, Proteus mirabilis. Other Enterobacteriacae in suppurative complications of diabetic foot syndrome were less frequent. Also anaerobes was detected in in patients with DFI [10].

Data on the frequency of main pathogens in DFI differ in Russian researchers. In the study of the frequency pathogens in a "Diabetic foot" office of South-Western District of Moscow it was shown, that it was dominated Gram-positive cocci (72%), which were presented mainly by staphylococci: S. aureus - 47%, other (coagulase negative) staphylococci - 23% [11]. S. aureus was isolated in 63.2% of cases in a Clinical Hospital at the Orenburg station for the period 2007-2012 [12].

In the study of the structure of pathogens in the department of wounds and wound infections the AV Vishnevsky Institute of Surgery in Moscow S. aureus was distinguished in 21.3-23.5% of cases while the number of S. epidermidis was identified from 17.0% to 14.3% cases for the period 2012-2015 [13].

The structure of the isolated microorganisms in patients with DFI, admitted to the clinic of North-Western State Medical University named after I.I Mechnikov, dominated by strains of S. aureus, amounting to about one-third of all isolates (31.6%). Staphylococcus epidermidis was detected in 16,3% cases [14]. In other regions of Russia S. aureus and coagulase-negative staphylococci are registered in 28% of cases [15].

Data on the frequency of detection of Enterococcus spp. ranged from 6.2% to 14,3-16% cases [14, 15, 16]. In the AV Vishnevsky Institute of Surgery the number of E. faecalis strains was increased from 6.5% to 16.0% for the period 2012-2015 [13]. According to researchers same regions of Russia E. faecalis is registered in 12% of cases, E. cloacae 16% of cases [17].

The frequency of gram-negative pathogens, represented mainly by Enterobacteriaceae and Pseudomonas aeruginosa, detected Russian researchers have varied. Among Gram-negative rods, amounted to only 28% out of all microorganisms, were dominated Enterobacteriacae (Proteus mirabilis, Escherihia coli, Klebsiella pneumoniae, Enterobacter spp., and others) in 12% cases, as well as non-fermentative bacteria (Pseudomonas aeuruginosa, Acinetobacter spp.) in 14% cases. In 5 patients (9%) were detected Pseudomonas aeruginosa [11].

According to the research team Division of wounds and wound infections AV Vishnevsky Institute of Surgery in patients with different forms of acute and chronic purulent infection in noninsulindependent diabetes mellitus, including DFI for the period of 2012-2015, was revealed a slight increase in strains of Gram-negative pathogens by Enterobacteriacae (Escherihia coli, Klebsiella pneumonia, Proteus mirabilis) from 3.2% to 12.6%, while the number of non-fermenting bacteria (Pseudomonas aeruginosa, Acinetobacter spp.) was decreased from 11.3 % to 7.6% strains [13]. In the structure of Gram-negative organisms, it was identified Pseudomonas aeruginosa (15.3%), Escherichia coli (9.2%) and Proteus mirabilis (6.1%) by researchers from St. Petersburg. Acinetobacter and Enterobacter were presented in small amounts (by 3.1%, respectively) [14].

During the analysis of pathogens structure in DFI in selected regions of the Russian Federation for the period 2009-2013, it was found that gram-negative microorganisms were determined in 29.3% of cases. It were predominated Pseudomonas aeruginosa (12.8%). Out of Enterobacteriacae were isolated Escherichia coli (6.1%), Proteus spp. (6.7%), Citrobacter diversus (2.4%), Acinetobacter baumannii in 2 cases (1.2%) [15].

Data on the frequency fungi varied from 2.4 % cases to 8.5% cases in the study different researches [13, 15].

The most common infecting microorganism isolated in in a tertiary care hospital in Jakarta was S. aureus (47.5%), followed by Pseudomonas spp. (16.9%), E. coli (10.2%), Streptococcus spp. (8.5%), Enterobacter spp. (7.0%), Proteus spp. (6.7%), and Acinetobacter spp. (3.2%). Overall, 37.2% of the diabetic foot infection caused by a single microorganism, and 62.8% had polymicrobial infections [18].

In a multicenter, prospective study conducted in Turkey showed that of the 522 strains isolated from patients with infectious complications of diabetic foot syndrome in 36.4% registered Gram-positive pathogens, of which prevailed S. aureus (11.4%). Gram-negative pathogens constituted 60.2% of all the cases, and most often identified microorganism was Escherichia coli (15%) [19].

In some researchers, the type of isolated microorganism depends on the depth of the ulcer process. Gram-positive cocci predominated in outpatient treatment of superficial diabetic ulcer or ulcer extension without abscess or osteomyelitis. According Wagner's classification the most common disease in this

patients was grade 1-2. In case more severe lesions (deep tissue infection, gangrene) increases the proportion of gram-negative bacteria and anaerobes. Gram-negative rods were found mostly in patients with chronic, previously treated wounds. In case previously inpatient treatment for 7-10 days it was showed the prevalence of gram-positive microorganisms: S. aureus – in 8 cases (33.3%), and coagulase-negative staphylococci – in 7 cases (29.2%). Gram-negative bacteria P. aeruginosa presented in 4 cases (20.8%), 1 strain of P. mirabilis (4,2%) was isolated. Candida fungi were inoculated in 3 cases (12.5%) Also, it was increased the average number of pathogens allocated from one patient [11, 12, 15].

It was shown by Russian researches that in patients were treated in the department of surgical infections during the year more than once, and had received previous at least one course of antibiotic therapy, structure of the microorganisms was significantly different compared with structure of the microorganisms ulcers in patients hospitalized first time. According Wagner's classification the most common disease was grade 3-4. The predominant species was Staphylococcus aureus, P. aeruginosa, A. baumanii. Biofilm was verified in 76% of patients hospitalized more than once a year, only 6% of hospitalized patients for the first time [10].

It was found, that the most frequent agent DFI in patient without surgical treatment was S. aureus, which had resistance to meticillin in 13.5% cases. There was a significant frequency of gram-negative rods in patients without surgical treatment. The vast majority of DFI in patients with previous surgical treatment are caused by S. aureus. Percentage of S. aureus, which had resistance to meticillin was significantly higher (39.3% cases). Also 1.5-2 times more common to appear Pseudomonas aeruginosa, Acinetobacter baumanii and Enterococcus faecalis, as compared with the primary patients [16].

Until the most recent decade, the majority of studies on the microbiology of DFI were conducted in North America and Europe. In recent years, investigations in warm climates (especially India, but also the Middle East and Africa) have found the most common isolates to be Gram-negative rods, particularly Pseudomonas aeruginosa. We can only speculate on the reasons for this disparity, but they may include a hot climate causing foot sweating, the use of poor footwear, a high incidence of patient self-treatment with antimicrobials, frequent foot washing, and suboptimal perineal/hand hygiene. Thus, clinicians in these regions should consider covering Enterobacteriaceae and Pseudomonas spp, pending culture and sensitivity results [12].

In recent years DFI caused by multidrug-resistant organisms, such as extended-spectrum beta-lactamase-producing Gram-negative rods or methicillin-resistant S. aureus (MRSA) have emerged as substantial problem. Infection with an antibiotic-resistant organism certainly requires the selection of an agent active against that isolate, but should not otherwise alter therapeutic management [20, 21].

Many researchers of Russia registered the highest level of methicillin resistant staphylococcus. The analysis sensitivity allocated pathogens in patients with different forms acute and chronic purulent infection in patient with diabetes mellitus, including purulent complications of diabetic foot for the period 2012-2015, being treated the AV Vishnevsky Institute of Surgery revealed the sensitivity of all isolated strains of gram-positive to vancomycin. It is shown that the number of MRSA decreased in 2015 to 43% against 48% in 2012, while the number of methicillin-resistant coagulase-negative staphylococci (methicillin-resistant S. epidermidis, MRSE) increased by 2.5 times - from 28% in 2012 to 71% in 2015 g. [13].

The level of MRSA in patients with DFI were treated in Smolensk and Smolensk region in 2005-2008. was 49% of cases [22]. According to study of the certain regions of Russia antibiotic susceptibility of grampositive strains recorded increase of resistance to oxacillin in isolated strains of S. aureus and coagulase-negative staphylococci for 2009-2013. It was shown the increase in the number of MRSA from 20% of cases in 2009 to 50% of cases in 2013. The same trend was observed among strains of coagulase-negative staphylococci. In 2009-2011 up to 25% of MR-CNS were isolated, in 2013 – up to 66.6% of resistant strains. In the case of incomplete eradication of infections and repeated bacteriological examination of hospitalized patients level of MRSA and MR-CNS is much higher than the initial, and ranged from 66.6% of cases in 2011 and 2012 to 100% in 2009 and 2013 [15]. undergoing in-patient treatment.

Some researchers have shown that on an outpatient treatment prevalence of MRSA was extremely high (62% of strains S. aureus). MR-CNS were less common: 29% out of coagulase-negative staphylococci. The proportion of methicillin-resistant staphylococci (MRSA + MR-CNS) among all agents was 35%. One out of 26 Staphylococcus aureus (3.8%) was resistant to vancomycin [11].

According to foreign authors, the level of S. aureus resistance to oxacillin ranged from 0% of resistant strains isolated from patients undergoing treatment of diabetic foot syndrome in the surgical department of Ouagadougou hospital (Burkina Faso) up to 100% resistance in strains isolated from patients, undergoing treatment at the central hospital in Mexico City [23, 24].

Data on the frequency of detection of Enterococcus spp. and its resistance vary greatly among different authors and 7,1- detected in 16% of cases detected Enterococcus spp. [13, 14, 15], which is a bit less than the level obtained by US researchers Lipsky B.A. et al., 2012 [25]. According to the authors from same regions the Russian Federation, enterococcus was not allocated in patients with DFI [14, 22].

Selected strains of Enterococcus spp. Russian researchers 52% were resistant to ampicillin at a detectable sensitivity to vancomycin [15]. According to Shailesh K. Shahi 71.4% strains of Enterococcus spp. were resistant to vancomycin [26].

It was shown by the researchers from Portugal that all isolates Enterococci were considered multidrug-resistant, cytolysin and gelatinase producers, and the majority also demonstrated the ability to produce biofilms. It was found that polymicrobial communities produced higher biofilm values than individual species. Pseudomonas + Enterococcus, Acinetobacter + Staphylococcus and Corynebacterium + Staphylococcus produced higher biofilm than the ones formed by E. faecalis + Staphylococcus and E. faecalis + Corynebacterium [27].

The high resistance level of P. aeruginosa was detected in some regions of the Russian Federation. It was shown resistance strains P. aeruginosa to amikacin in 64.5% strains, ciprofloxacin - 96% strains, imipenem - 69% strains, ceftazidime - 33% strains. High levels of resistance are characterized isolates of A. baumanii that was resistant to amikacin in 68% of cases, ciprofloxacin - 99% of cases, imipenem - 82% of cases, ceftazidime - 33% of cases. All non-fermenting bacteria isolated strains showed sensitivity to meropenem [28].

In some regions of Russia Pseudomonas aeruginosa sensitivity to antibiotics was registered an increase in resistance level to β-lactams. Thus, the sensitivity to cefepime reduced from 100% in 2009-2011 up to 33.3-66.6% in 2012-2013, at the same time there revealed a low sensitivity to ceftazidime, which was 50% in 2009, and 33.3% in 2011-2013. All isolated strains of P. aeruginosa showed sensitivity to meropenem and imipenem, except for one strain isolated in 2012, resistant to meropenem. We revealed a low sensitivity of P. aeruginosa to amikacin and gentamicin: from 0% of strains isolated in 2010-2011 up to 50% of strains isolated in 2012-2013 were susceptible to amikacin. Sensitivity to gentamicin varied from 33.3% to 66.6% at the preserved sensitivity to netilmicin, which ranged from 66.6% up to 100%. We recorded a low level of sensitivity to fluoroquinolones: P. aeruginosa sensitivity to ciprofloxacin ranged from 50% to 66.6%, with the exception of strains isolated in 2011, which showed 100% sensitivity. We revealed a reduction in sensitivity to levofloxacin from 100% in 2009-2010 up to 50-66.6% in 2011-2013 [15].

In comparison with the data by Privolnev V.A., 2011, there was an increase in Pseudomonas aeruginosa resistance to cephalosporins, fluoroquinolones and aminoglycosides, in contrast to, in particular, netilmicin and less amikacin and gentamicin revealed in the studied period [22].

According to the researchers of the Vishnevsky Institute of Surgery among gram-negative bacteria was a slight increase in the number of Enterobacteriaceae while the number of P. aeruginosa was reduced. All isolates of P. aeruginosa showed sensitivity to colistin, piperacillin / tazobactam [13].

In patients were hospitalized in the clinic of North-Western State Medical University named after I.I Mechnikov, St. Petersburg P. aeruginosa was revealed resistance to gentamicin (66.7%), ceftazidime (53.3%), ciprofloxacin (46.7%), amikacin (33.3%). The highest activity was detected in imipenem, which revealed 22.0% of resistant strains [14].

Data on Russian researchers in hospitalized patients not subjected to a complete eradication strains of Pseudomonas aeruginosa revealed on repeated bacteriological examination having showed the presence of a reduced sensitivity to cephalosporins, ranging from 0% to 100% at the preserved high sensitivity to imipenem – in 100% of cases. Sensitivity to meropenem was found in 50% of P. aeruginosa strains, and variative sensitivity to gentamicin and amikacin was recorded. In 2010-2011 the amikacin-resistant strains were revealed. In 2009 and 2012-2013 up to 50% of strains staying susceptible to amikacin with continuously reducing sensitivity to fluoroquinolones, which was 100% in 2011, 50% in 2012, 100% for ciprofloxacin and 0% for levofloxacin in 2013. These high variations in sensitivity values are, probably, due to a small number of isolated strains and identify a trend of the developing resistance [15].

Identification of resistant strains of P. aeruginosa under incomplete eradication is consistent with Chinese researchers, who showed the relationship between multi-resistant microflora isolated in patients with DFI, and a higher incidence of amputation in 33.3% of cases as compared with 8.7% of amputations in case of strains with no signs of multi-resistance [30].

Identified strains of Acinetobacter baumannii in the 1.4% -4.2% of cases showed a high level of resistance to different groups of antibacterial drugs. Revealed resistance to penicillins, cephalosporins, fluoroquinolones, aminoglycosides. In 100% of the marked sensitivity of the microorganism to carbapenems [13, 14, 15, 17, 29].

Carbapenemases in Enterobacteriaceae are not detected in most regions of Russia and isolated strains showed sensitivity to carbapenems [11, 12, 13, 14, 15, 22, 31].

In some regions registered resistance K. pneumoniae to imipenem up to 18% of cases with persistent sensitivity to meropenem [29].

Many authors shows the growing resistance of pathogens Enterobacteriacae to cephalosporins, due to the production of β-lactamase-producing extended spectrum (ESBL) [13, 22]. Especially many (70%) strains producing ESBL were among K. pneumoniae. Among the amount of E. coli ESBL producers has increased from 32% to 45%. It showed a high level of resistance of Enterobacteriaceae to fluoroquinolones in K. pneumoniae, E. coli, P. mirabilis [13].

According to researchers of Smolensk P. mirabilis resistant to cephalosporins was 36,4% E. coli to cefotaxime, ceftazidime - 40%, cefepime - 46.7% [22].

In a study of the sensitivity of Enterobacteriaeae in the clinic of North-Western State Medical University named after I.I Mechnikov in the period 2009-2012 among strains of E. coli were resistent to amoxicillin / clavulanate were 44.4%, to ciprofloxacin and cefotaxime 33.3%, respectively. Among the P. mirabilis resistant to amoxicillin / clavulanate was 50% of the strains to ciprofloxacin - 33.3% of the strains.

According to some authors identified E. coli and other enteric bacteria were sensitive to all antibiotics used, which may indicate infection of the wound with diabetic foot syndrome in the community [11].

It was detected by the authors of the some regions of the Russian Federation Enterobacteriaceae were resistant to gentamicin at the continuing sensitivity to other antibacterial agents [15].

It is shown that an increase in the number of hospital admissions has changed not only the bacterial spectrum of wounds, but also the resistance of pathogens to antibiotics, one reason for that is a bacterial film [32].

In the study of the Zaporozhye researchers the cause of pyo-necrotic complications of DFI were gram-positive flora in 56,9% of cases, in 33,3% – gram-negative, in 2,9% – anaerobes, in 2,3% – fungi. The phenomenon of resistance to the major antimicrobial drugs was revealed in 65 (37,4%) bacteria. Pseudomonas aeruginosa, Staphylococcus aureus, Staphylococcus epidermidis, Esherihia coli, Acinetobacter baumannii, Enterococcus faecalis had the greatest resistance. Among the groups with the identified Pseudomonas aeruginosa, 66,0% of the bacteria were characterized by a phenotype of resistance to carbapenems, 33,0% of which were panresistant ones. In patients with Staphylococcus aureus in 60,5% of cases the gene of MRSA with three genetic variations differed by resistance to certain groups of antibiotics was revealed. The most important was panresistant one (4,3%) [33].

According Indian researchers antibiotic susceptibility test of 142 aerobic bacteria revealed that 38 (26.76%) were resistant to antibiotics belonging to three or more classes. Henceforth, these 38 isolates were designated as MDR bacteria. Prevalence of resistance to different antibiotics among the isolates was; cefazolin (65.78%), cefoxitin (73.68%), cefoperazone (34.21%), cefepime (68.42%), gentamycin (94.73%), amikacin (50%), kanamycin (92.10%), streptomycin (65.78%), spectinomycin (73.52%), piperacillin/tazobactam (26.31%), ampicillin (89%), clindamycin (34.21%), tetracycline (60.52%), meropenem (76.31%), trimethoprime (63.15%), and co-trimoxazole (76.31%). 71.4% of Enterococcus spp. were resistant to vancomycin whereas all the Staphylococcus spp. were resistant to methicillin [34].

According to Pakistani investigators Pseudomonas aeruginosa were isolated from 34.8% of patients and was sensitive to ceftazidime, imipenem, ciprofloxacin and gentamicin in 2009-2011 [35].

In the research of ciprofloxacin concentrations in the interstitial fluid of patients infectious diabetic foot complications during microdialysis was showed that after intravenous administration of 0.2 mg of ciprofloxacin revealed no significant differences in its penetration into the inflamed and unaffected tissue. [36]

According to German researchers in the study of the degree of penetration of levofloxacin in affected tissues in patients with diabetic foot syndrome it was shown that after oral treatment of levofloxacin concentration in wound necrotic tissue was 2.33-23.23 mg / kg and 0.12-6.41 mg / L in plasma. Tissue-to-serum ratios of levofloxacin concentrations were >1.0 [37].

In the study moxifloxacin penetration by intravenously or orally once a day at a dose of 400 mg per day was determined in tissue samples of infected necrotic wounds resected diabetic foot after

4-8 days of treatment. Average concentrations of moxifloxacin in the necrotic tissue of infected diabetic foot wounds after orally or intravenously amounted to 1,79 ± 0,82 and 2,20 ± 1,54 g / g, which exceeds the minimum inhibitory for Staphylococcus aureus and Escherichia coli [38].

In the research of Hamada Y. and others, 2015 showed that the concentration of vancomycin in serum and interstitial tissue using microdialysis shown that the degree of penetration was 1.91 and 0.85 in the plasma and tissues. The authors concluded that the standard dose of vancomycin provide a low probability of obtaining targeted pharmacodynamic effects in the tissue of the lower limbs, connected with the wide variability in the tissue penetration of vancomycin in infectious complications of diabetic foot syndrome and cannot be predicted on the basis of determining the concentration of vancomycin in the blood [39].

When linezolid pharmacokinetic study demonstrated that the concentration after 8 hours and the maximum concentration (Cmax) were observed in plasma higher concentration (65,5 ± 21,2 mg * h / L and 16.4 ± 4.6 mg / L) as compared to inflamed (36,3 ± 22,9 mg * h / l and 6.6 ± 3.6 mg / l) and non-inflamed tissue (33,0 ± 17,7 mg * h / l and 6.7 ± 3.6 mg / l). These data show good penetration of linezolid into tissues infectious complications of the diabetic foot, but the therapeutic effect can occur delayed [40].

A study of linezolid concentrations in infected tissues and blood plasma in patients with isolated Staphylococcus aureus. This research characterized by a reduced susceptibility to vancomycin in patients with peripheral vascular disease and infectious complications, requiring surgery. It is shown that the concentration of linezolid in the tissues of 51% (from 18% to 78%), leads to the conclusion that the effectiveness of linezolid in the treatment of MRSA patients with diabetic foot with reduced concentrations of the drug at the site of blood flow disturbances [41].

It has been studied the pharmacokinetics and pharmacodynamics of linezolid and trimethoprim / sulfamethoxazole high (320/1600 mg) and standard (160/800 mg) dose. For the average ratio of linezolid tissue / plasma was 0.46 with a standard dose of 1.2 and at a high dose. For trimethoprim is 0.23 and 0.36 respectively. The data obtained showed good penetration in soft tissue in patients with DFI and bactericidal activity against Staphylococcus aureus and β-haemolytic streptococci [42].

In the Austrian researchers demonstrated in patients with osteomyelitis applying microdialysis equilibrium between the plasma and tissue concentrations of daptomycin in the application in plasma reached approximately 2 hours after infusion. When this ratio average area under the pharmacokinetic curve (AUC) for the plasma AUC tissue after 16 hours reached 1.44 for healthy tissue to 0.98 inflamed subcutaneous adipose tissue and bone to 1.08. These results can be regarded as an effective means of treating patients with infectious complications of diabetic foot and osteomyelitis [43].

In the study of tissue concentrations of ceftazidime dose of 2 g bolus injected intravenously 30 minutes before surgery in patients with diabetes and without undergoing lower limb amputation, showed no difference in the concentration of ceftazidime. As a result of multiple regression analysis showed that the main factor determining the concentration in the bone and soft tissues is tissue perfusion, which will amount to 40-47% concentration in the studied tissues [44].

It is shown that the introduction of ertapenem intravenously at a dose of 1.0 after 8 hours ego concentration, determined at a microdialysis in the soft tissues in patients with DFIs did not differ from the registered concentration in healthy volunteers [45].

When studying tigecycline degree of penetration into the bone tissue revealed that the ratio of the bone tissue / serum was 4.77, which confirms the penetration of tigecycline into bone tissue [46].

Thus, in the clinic of infectious complications of the diabetic foot are important microbiological population-geographical features of the studied pathology. These researchers necessitate constant of at the local level of microbiological monitoring of the structure of pathological agents with the assessment of the sensitivity of the microorganisms allocated to the appointed treatment in the early stages of infectious complications of diabetic foot infections according to the degree of penetration of antimicrobial chemotherapeutic agents in bone and soft tissue low limbs.

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