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# Rational Antibiotic Therapy of Trophic Lesions of Lower Extremities of Various Etiology.

**Aralova MV*, Alimkina YN, and Gluhov AA.**

N.N. Burdenko Voronezh State Medical University,10 Studencheskaia Str.,Voronezh, 394036, Russian Federation.

**ABSTRACT**

Treatment of trophic ulcers is a complex multidisciplinary task. The emergence of purulent-necrotic complications is associated with a violation of the barrier function of the skin due to changes in trophism and its micro-fall. Insufficiency of arterial blood supply, venous and lymphatic stasis, promotes the development and spread of infection. When the process is heavier, the depth and area of the trophic defect increase, a purulent wound discharge appears. Often, patients are associated with the phenomenon of purulent-resorptive fever, which may indicate the progression of the disease and the development of a systemic inflammatory reaction. The purpose of antibiotic therapy in the complex treatment of trophic ulcers is indicated in the presence of a clinic of a systemic and / or severe local inflammatory reaction. The data of the microbial spectrum, the dynamics of its change in the study of wound detachable in patients with trophic ulcers, the sensitivity analysis of isolated strains of microorganisms to antibacterial drugs are analyzed. Schemes for prescribing antibacterial drugs are given, taking into account the severity of the lesion and the risk of detection of resistant pathogens based on data from different authors, national recommendations on antibiotic therapy and own observations.

**Keywords**: trophic ulcers, microorganisms, antibacterial therapy.

***Corresponding author***

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## INTRODUCTION

On the surface of human skin, various microorganisms are colonized. The main representatives are coagulase-negative staphylococci (epidermal, saprophytic), lipophilic and non-lipophilic corynebacteria, anaerobic propionobacteria. Less common are coagulase-positive staphylococci (Staphylococcus aureus), gram-negative bacteria (enterobacteria). In the absence of damage to the skin, normal microflora does not cause pathological changes. The emergence of purulent-necrotic complications is associated with a violation of the barrier function of the skin due to changes in trophism and its microdisplay [1,8,12].

To the occurrence of trophic ulcers can lead to various diseases. The key moment in the development of a peptic ulcer defect is deep disruption of trophic processes, which leads to the formation of a necrobiosis zone and perifocal edema, inflammation, progressive impairment of microcirculation and innervation [2,18].
The trigger mechanism for the development of a trophic defect can be: insect bites, traumatic effects, cracks and skin rash. As a result, the inflammatory reaction of soft tissues begins to develop.
This is especially important in patients with the defeat of arterial and venous blood flow with the phenomena of pronounced metabolic disorders, edema.

The presence of such factors as insufficient arterial blood supply, venous and lymphatic stasis, promotes the development and spread of infection with the formation of inducible cellulite. When the process is heavier, the depth and area of the trophic defect increase, a purulent wound discharge appears. Often, patients are associated with the phenomenon of purulent-resorptive fever, which may indicate the progression of the disease and the development of a systemic inflammatory reaction. With bacterial aggression, an insufficient local response, the area of the trophic defect widens, the processes of fibrosis of the skin and subcutaneous tissue take place in the soft tissues, which closes the vicious circle by the progression of microcirculatory disturbances, venous and lymphatic outflow [2,8,12].

In connection with a large number of pathological factors contributing to the maintenance of the trophic peptic ulcer defect, the treatment of such patients presents a complex multidisciplinary task consisting of two main areas: correction of the underlying disease and a complex effect on the trophic defect [3].

Often, doctors dealing with the treatment of such patients, there is a natural question: "Is antibiotic therapy shown to patients with trophic ulcers?" The study of literary sources does not give clear indications of the decisive influence of pathogenic microflora in the development and progression of trophic ulcers, and it is also noted that the appointment of antibiotics does not significantly accelerate the healing time [2,5]. However, the fact that the disruption of normal symbiotic relationships of the saprophytic microflora of the skin leads to a decrease in local colonization resistance ("local immunity") and the progression of trophic skin disorders, and sometimes also a systemic inflammatory reaction [2].

With the long-term existence of trophic ulcers, almost all patients can develop perifocal dermatitis, pyoderma, eczema, erysipelas due to exposure to the skin of abundant wound detachable and various dressings and bandages. Secondary microbial damage to deep layers of skin with penetration of staphylococcal infection leads to the formation of purulent folliculitis, impetigo and erosion, which can lead to an increase in the size of the ulcer. Thus, the appointment of antibacterial therapy in the complex treatment of trophic ulcers is indicated in the presence of a clinic of a systemic and / or severe local inflammatory response. Preparations of starting antibacterial therapy are usually penicillins, fluoroquinolones, cephalosporins and additionally - preparations of imidazole series (metronidazole). In local treatment, antibacterial ointments are used [2,6,12,13]. The standard duration of antibiotic therapy for trophic ulcers is 7-10 days.

Investigation of the microbiological composition of wound detachable trophic ulcers routinely in outpatient practice, as a rule, does not produce, whereas the choice of rational antibiotic therapy largely depends on the type of the isolated pathogen.

The causative agents of a greater number of purulent-septic diseases are still staphylococci. They are usually sensitive to beta-lactam antibiotics, macrolides, rifampicin, co-trimoxazole, fusidin, phosphomycin, clindamycin. Some strains of staphylococci carry a resistance gene to beta-lactams [19]. The marker of this type of resistance is resistance to oxacillin. According to the multicenter study CERBERUS, in which methicillin-resistant staphylococci were studied in 36 large cities of Russia, the specific gravity of staphylococcus aureus

resistant to oxacillin (methicillin) ranged from 13 to 75%. The level of methicillin resistance of epidermal staphylococcus (S. Epidermidis) is from 11 to 91%. Most epidermal staphylococcus is not the causative agent of infection, but only contaminates the biomaterial, but its isolation in immunocompromised patients can be of clinical importance and require the appointment of appropriate antibiotic therapy [11,13,22].

"Problem" microorganisms are also enterobacteria that produce beta-lactamases of the extended spectrum (ESBL) and multidrug-resistant pseudomonas. These pathogens retain high sensitivity only to inhibitor-protected antisseinemic beta-lactams: piperacillin/tazobactam, cefoperazone/sulbactam. A growing percentage of strains of gram-negative microorganisms resistant to carbapenems (meropenem, imipenem) [12,15,16,20].

Wound infection of trophic ulcers has a direct toxic effect on surrounding tissues, reduces local and general immunity, causing specific microbial sensitization of the organism, exacerbating trophic disorders. Considering all of the above, in the first phase of the wound process of trophic ulcers, the results of bacteriological investigation play the main role determining the tactics of treatment and, first and foremost, the choice of an antibacterial preparation [3,8].

The commonly used methods for determining the type of microorganism and its antibiotic resistance, respectively, allow to obtain the result only on day 3, therefore, for a valid empirical choice of an antibacterial preparation, data of local microbiological monitoring of species composition and antibiotic resistance of pathogens are needed.

It is also important to stratify patients by the severity of the condition and the degree of risk of resistant pathogens and to apply de-escalation tactics of antibiotic therapy. In the absence of risk factors for resistant flora for empirical antibacterial therapy, you can choose: inside - cefuroxime, amoxicillin/clavulanate; parenteral – cefazolin +/- ceftazidime; amoxicillin/clavulanate +/- ceftazidime. In case of a serious condition, the presence of risk factors for resistant pathogens (previous antibiotic techniques, contacts with medical institutions, immunosuppressive therapy, etc.), the drug of choice should overlap all potential pathogens, taking into account their probable resistance: parenteral carbapenems (ertapenem, meropenem, imipenem, doripenem) or inhibitor-protected anti-synergistic beta-lactams (piperacillin/tazobactam, cefoperazone/sulbactam) + antibiotic with anti-MRSA activity (ceftarolin, daptomycin, linezolid or vankomycin). In monotherapy, tigecycline can be used in patients of moderate severity, if there is no risk of pseudomonas (including Pseudomonas) infection. With mild and moderate severity of the condition, antibacterial therapy with oral medications is possible, in severe cases, intravenous antibiotics are indicated [9,10,13,21].

After identifying the pathogen and obtaining an antibiotic image, an evaluation of the antibiotic therapy should be conducted. When isolating from the wound detachable oxacillin-sensitive staphylococcus, the choice of drugs may be beta-lactam antibiotics. In the arsenal of the doctor there are enough drugs for both oral and parenteral route of administration: cephalexin, cefuroxime, oxacillin, cefazolin, amoxicillin/clavulanate, ampicillin/sulbactam. Cephalosporins of the third generation (cefotaxime, ceftriaxone, cefoperazone, ceftazidime, cefoksitin) have insufficient antistaphylococcal activity [9,10,11].

With the resistance of staphylococci to oxacillin, all beta-lactam antibiotics (penicillins, cephalosporins, carbapenems, monobactams) are ineffective [4]. Often there is a concomitant resistance of methicillin-resistant staphylococci to macrolides, tetracyclines, fluoroquinolones, lincosamides, rifampicin. The drugs of choice in such cases are: vancomycin, linezolid, ceftarolin, daptomycin, tigecycline, telavancin. [4,9,13]. Antibiotics of other groups - fluoroquinolones, fosfomycin, fusidine, rifampicin, macrolides, sulfonamides - can be prescribed only with confirmed sensitivity of the pathogen. Thus, the choice of adequate antibiotic therapy in cases of oxacillin/methicillin-resistance is significantly hampered. The task is complicated by the fact that linezolid and tigecycline have only a bacteriostatic effect. In conditions of impaired microcirculation, delivery of drugs to the lesion site suffers and bacteriostatic antibiotics may not be effective. Drugs with bactericidal action, approved for use in skin and soft tissue infections, are few: vancomycin, daptomycin, ceftaroline and telavantcin. However, in recent years in Russia and abroad, most strains of MRSA have a reduced sensitivity to vancomycin, which leads to its clinical inefficiency when using the standard dosage regimen of the drug. The detection of this type of resistance is carried out using the E-test, which allows to determine the minimum suppressive concentration of vancomycin. In cases of isolation of strains

with reduced sensitivity to vancomycin, its administration in a dose of 3-4 g / day is possible. Studies of efficacy and safety in trophic ulcers of different etiologies were not conducted. Possible toxic, especially nephrotoxic, complications with this mode of dosing vancomycin in patients with risk factors. In addition, it must be taken into account that vancomycin is not active against ordinary, sensitive to oxacillin, strains of staphylococci, which does not allow it to be included in empirical antibiotic therapy as a universal antistaphylococcal drug. Unlike vancomycin, new drugs with anti-MRSA activity (daptomycin, ceftaroline, telavancin) work equally well for both MRSA and the strains of staphylococcal-sensitive strains (MSSA) [4,9,17].

Resistance to ceftazidime is a marker for the production of extended-spectrum beta-lactamases. If ceftazidime resistance is detected in enterobacteria, cephalosporins (I-IV generations) should not be used, even in cases of their laboratory-confirmed sensitivity [17]. The drugs of choice can be piperacillin/tazobactam, cefoperazone/sulbactam. When detecting resistance to carbapenems, it is advisable to use high doses of anti-synergic carbapenems (imipenem, meropenem, doripenem) by prolonged infusions with additional administration of beta-lactamase inhibitors (or preparations containing them). When pseudomonads are isolated from trophic ulcers, it is also necessary to take into account the antibioticogram data [4,7,9,13,21]. Drugs of alternative choice for the isolation of multidrug-resistant gram-negative pathogens (enterobacteria, pseudomold) can be polymyxin-B preparations for parenteral and topical application [7,9,13].

In connection with the violation of microcirculation, it is preferable to administer maximal doses of antibiotics and use the intravenous route of administration, so patients with trophic ulcers of the lower extremities must stop in order to stop the infectious process [23].

As a local therapy in addition to systemic antibacterial therapy, bacteriophage preparations, antiseptics can be used. It is expedient to determine the sensitivity of pathogens to bacteriophages, since some of the pathogens to them can be insensitive. Local use of most antibiotics in the form of cheating, suction of the wound surface is not advisable: under the action of an acidic environment of wound detachable trophic ulcers, they are quickly cleaved and inactivated [4,9].

Thus, in the first phase of the wound process, the results of bacteriological investigation of trophic ulcers play a major role in determining the tactics of treatment and, first of all, the choice of an antibacterial preparation.
The increased level of resistance of microorganisms requires stratification of patient groups and a differentiated choice of antibiotic therapy regimens. Antibacterial therapy of suppurative complications of trophic ulcers is preferably performed in a hospital in combination with intensive therapy of the underlying disease, with parenteral administration of drugs.

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