

The approaches to the choice of starting antibacterial agents in patients with diabetic foot syndrome undergoing inpatient treatment in St. Joseph Belgorod Regional Clinical Hospital

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Abstract

Background and Objective: 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. **Methods:** It was found, that in patients with diabetic foot infection dominated Gram-positive microorganisms (62.7%). It was detected *Staphylococcus aureus* (23.4%), *Staphylococcus* spp. (25.8%), and *Enterococcus* spp. (14.5%). Among the Gram-negative aerobes, *Pseudomonas* spp. was the more frequently isolate (14.5%). Enterobacteriaceae were detected in 18.5% cases. *Candida* spp. was isolated in 1.6% cases. It was dominated Gram-positive cocci in Wagner Grade I-III: *S. aureus* was isolated in 36.34% - 23.89% cases; *Staphylococcus* spp. was detected in 22.22% - 28.94% cases; *Enterococcus* spp. was determined at 8.33% - 18.5% cases in Wagner Grade IV and V was found increased amount Gram-negative rods from 39.18% to 63.63%, respectively. It was presented Enterobacteriaceae spp. and *Pseudomonas aeruginosa*. **Results:** The analysis of antibiotic susceptibility of Gram-positive strains recorded increase of resistance to oxacillin in isolated strains of *Staphylococcus* spp. (*S. aureus* and coagulase-negative staphylococci) from 25% to 100% in Wagner Grade I and V, respectively. In Wagner Grade IV and V was detected Enterobacteriaceae producing extended spectrum beta lactamase in 75% (*Escherichia coli*, *Klebsiella pneumoniae*, and *Citrobacter diversus*) and 83.3% (*E. coli*, *Proteus vulgaris*, and *K. pneumonia*) cases, respectively. Studying the *P. aeruginosa* sensitivity to antibiotics in Wagner Grade IV and V was registered decrease susceptibility to ceftazidime in 36.36% and 0%, meropenem in 85.7% and 50%, levofloxacin in 68.18% and 50%, ciprofloxacin in 54.54% and 50%, and amikacin in 42.7% and 33.3%, respectively. **Conclusion:** It is discussed the approaches to the choice of starting antibacterial agents depend on the structure of pathogens and their sensitivity to antibiotics in patients with diabetic foot ulcers with different Wagner grades in patients with diabetic foot syndrome undergoing inpatient treatment in St. Joseph Belgorod Regional Clinical Hospital.

Key words: Antibiotic resistance, antibiotics, diabetic foot syndrome, infection

INTRODUCTION

Diabetes mellitus (DM) is one of the most common high-cost chronic diseases and the most acute medical and social problem. Over the past decade, the world number of patients with DM 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 DM is insulin resistance, which is the cause of many metabolic disorders,

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Received: 04-07-2017

Revised: 29-07-2017

Accepted: 10-08-2017

including hyperglycemia, hypertriglyceridemia 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 DM 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.^[4-12]

The aim of this study is the determination of antibiotic agents for the treatment patients with diabetic foot infections (DFI) on admission.

Objectives of the Study

1. To study the structure of pathogens to antibiotics in patients with DFI undergoing inpatient treatment in the Department of Purulent Surgery of St. Joseph Belgorod Regional Clinical Hospital in 2014-2015 in different Wagner grades.
2. To study the sensitivity of pathogens to antibiotics in patients with DFI undergoing inpatient treatment in the Department of Purulent Surgery of St. Joseph Belgorod Regional Clinical Hospital in 2014-2015 in different Wagner grades.
3. To determine the antibacterial chemotherapeutic agents for initial antibiotic therapy of foot infections in diabetic patients in the Department of Purulent Surgery of St. Joseph Belgorod Regional Clinical Hospital depend on the structure of pathogens and their sensitivity to antibiotics in patients with diabetic foot ulcers with different Wagner grades.

METHODS

During 2014-2015, there were 207 patients with diabetic foot syndrome treated in the Department of Purulent Surgery of St. Joseph Belgorod Regional Clinical Hospital, 61.2% of them were men and 38.8% - women. The average age of patients was 58.9 ± 6.8 years old, the average length of inpatient stay in hospital - 28.3 ± 4.3 bed-days. Out of all patients, 98.6% patients suffered from DM type 2.

The diagnosis of diabetic foot syndrome and its complications were verified based on a comprehensive survey including data from clinical and laboratory researchers, duplex scanning of arteries of the lower extremities, transcutaneous oximetry, and bacteriological tests of necrotic tissue. For determination of clinical forms of diabetic foot syndrome the classification proposed by Dedov *et al.* in 2015, was used.^[1]

Foot ulcer was graded according to Wagner's classification: Grade 0, high-risk foot; Grade I, superficial ulcer; Grade II, deep ulcer penetrating to tendon, bone, or joint; Grade III, deep ulcer with abscess or osteomyelitis; Grade IV, localized gangrene; and Grade V, extensive gangrene requiring a major amputation.^[13]

According to the type of diabetic foot syndrome, we revealed neuropathic and neuroischemic variants of the diabetic foot syndrome. The most common were neuropathic type of diabetic foot syndrome. It was determined in 58.6% of patients/neuroischemic type of diabetic foot syndrome was found in 41.4% of patients.

The Wagner classification rates of patients with DFU in the Department of Purulent Surgery of St. Joseph Belgorod RCH were as follows: Grade I: 21 (10%), Grade II: 53 (25.7%), Grade III: 73 (33.3%), Grade IV: 48 (23.2%), and Grade V: 12 (5.71%).

Material for bacteriological examination was sampled on admission of the patient to the department for treatment. The identification of microorganism strains obtained from the wounds of patients with diabetic foot syndrome being treated in the Department of Purulent Surgery of Saint Joseph Belgorod RCH in 2009-2013. The sensitivity of microorganisms was determined by disk diffusion. Interpretation of the results was performed according to EUCAST criteria. The calculations were carried out with the "Statistica 10.0" applied statistical software package.

RESULTS

In our study of the positive cultures were polymicrobial and out of 207 positive cultures, 372 microorganisms were isolated. One microorganism was isolated in 20.28% cultures, polymicrobial cultures were detected in 79.71% positive cultures. Polymicrobial cultures were dominated in patients with Wagner Grade III-V. It was found that Gram-positive microorganisms (62.7%) dominated in patients with DFI. It was detected *Staphylococcus aureus* (23.4%), *Staphylococcus* spp. (25.8%), and *Enterococcus* spp. (14.5%). Among the Gram-negative aerobes, *Pseudomonas* spp. was the more frequently isolate (14.5%). The others Gram-negative microorganisms also isolated were *E. coli* (6.5%), *Proteus* spp. (4.0%), *Citrobacter diversus* (3.2%), *Morganella morganii* 2.4%, *Acinetobacter baumannii* (2.4%), and *M. morganii* 1.6%. *Candida* spp. was detected in 1.6% cases, which is consistent with data from other researchers.^[14-16]

The findings showed the prevalence of Gram-positive cocci (66.66%) in Grade I. It was identified *S. aureus* in 36.11% cases, coagulase negative staphylococci in 22.22% cases, and *Enterococcus* spp. in 8.33% cases. Gram-negative rods (36.34%) presented Enterobacteriaceae: *E. coli* (16.7%), *C. diversus* (11.1%), and *Proteus* spp. (5.55%).

The analysis of structure microorganisms in Grades II and III was shown Gram-positive strains isolated in 63.63% and 71.06% cases, respectively. Gram-negative strains were detected in 33.33% and 26.31% cases, respectively.

Among Gram-positive cocci *S. aureus* identified in 27.08% cases and 23.89% cases, coagulase negative staphylococci - in 23.95% and 29.2% cases, *Enterococcus* spp. in 14.6% and 18.5% cases in Grade II and III, respectively. Frequency of *Enterococcus* spp. is a bit less in Department of Purulent Surgery of St. Joseph Belgorod RCH than the level obtained by US researchers Lipsky *et al.*,^[17] but exceeds the number of isolated strains according to data by Privolnev.^[14]

In patients with Grades II and III Gram-negative organisms were presented Enterobacteriaceae and *Pseudomonas aeruginosa*. Among Enterobacteriaceae, it was detected *E. coli* (11.5%), *Enterobacter* spp. (2.1%), *Proteus* spp. (2.1%), and *Moraxella* spp. (1.05%) in Grade II. It was isolated *E. coli* (8.77%), *Proteus* spp. (2.63%), and *Enterobacter* spp. (2.63%) in Grade III. *P. aeruginosa* was identified in 15.62% and 11.4% cases in Grade II and III, respectively. *Candida albicans* was recorded in 2.08% and 1.76% cases in 2 and 3 grades, respectively.

It was found increase frequency of Gram-negative microorganisms to 38.73% cases in patients with Grade IV depend on Wagner's classification. Among Gram-negative rods, it was detected *P. aeruginosa* (23.15%), and Enterobacteriaceae were presented by *E. coli* (4.21%), *K. pneumonia* (4.21%), *M. morganii* (1.05%), and *C. diversus* (3.15%). Gram-positive cocci (60.82%) were presented *S. aureus* (20.43%) cases, coagulase negative staphylococci (29.03%), and *Enterococcus* spp. (11.82%).

The most severe degree of lesion feet according to Wagner classification Grade V is characterized by a predominance of Gram-negative flora (63.63%). It was isolated *Proteus vulgaris* in 18.75% cases, *P. aeruginosa* - in 18.75% cases, *E. coli* in 9.38% of cases, and *A. baumannii* in 6.25% of cases. Gram-positive pathogens identified in 36.37% of cases: *S. aureus* (21.8%), coagulase-negative staphylococci (9.37%), and *Enterococcus* spp. (6.25%).

The analysis of antibiotic susceptibility of Gram-positive strains recorded increase of resistance to oxacillin in isolated strains of *S. aureus* and coagulase-negative staphylococci in more severe tissue damage in patients with diabetic foot ulcer [Figure 1]. It was shown the increase in the number of methicillin-resistant strains of *S. aureus* from 30.7% and 34.61% cases in Grade I and II, respectively, to 55.5% and 63.15% cases in Grade III, and IV, that is less than the level of resistance revealed by domestic authors in the period until 2011.^[14] 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

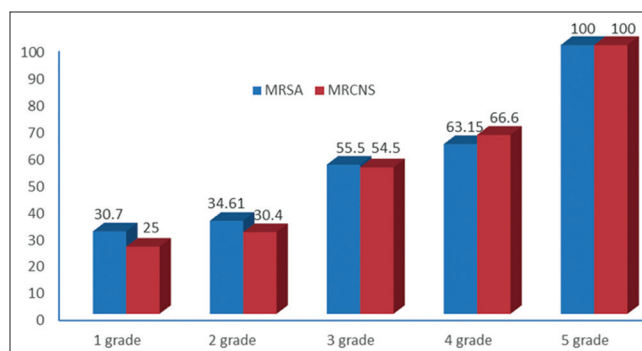


Figure 1: Percentage of isolated methicillin resistant strains of *Staphylococcus* in patients with diabetic foot syndrome on admission in Wagner's grade classification in 2014-2015

hospital (Burkina Faso) up to 100% resistance in strains isolated from patients, undergoing treatment at the central hospital in Mexico City (Table 1).^[18,19]

The same trend was observed among strains of coagulase-negative staphylococci. In patients with I and II Grade, it was allocated 25% and 30.4% methicillin-resistant strains, respectively, with Grade III and IV were verified 54.5% and 66.6% of strains resistant to oxacillin, respectively. All strains of *S. aureus* and *Staphylococcus* spp., which were isolated in V Grade, were methicillin-resistant.

The analysis of antibiotic susceptibility of *Enterococcus* spp. was shown that all of the isolates were susceptible to ampicillin in Grade I and II. Susceptibility to ampicillin was retained in 50% cases and 66.6% cases in 3 and 4, respectively. In patients with Grade V, all strains *Enterococcus* spp. were resistant to ampicillin and at a detectable sensitivity to vancomycin.

All strains of Enterobacteriaceae were sensitivity to amoxicillin/clavulanate, cephalosporins, carbapenems, fluoroquinolones, and amikacin in Grade I. All of registered Enterobacteriaceae strains were susceptible to amoxicillin/clavulanate, cephalosporins, carbapenems, fluoroquinolones, amikacin, except 2.63% strain of *E. coli* in Grade II, and 3.03% of strain *E. coli* in Grade III, which were produced beta-lactamase extended spectrum. We found these pathogens resistant to amoxicillin/clavulanate, cephalosporins. The strain of *E. coli*, isolated in Grade III was also resistant to ciprofloxacin and amikacin with preserved sensitivity to carbapenems.

In Grade IV was allocated 75% of strains of Enterobacteriaceae producing beta-lactamase extended spectrum: Strains of *E. coli* (3.22%), *K. pneumonia* (4.03%), and *C. diversus* (1.07%) found resistance amoxicillin/clavulanate, cephalosporins when the stored sensitivity to carbapenems. *K. pneumonia* and *C. diversus*, which were found, preserved susceptibility to fluoroquinolones, amikacin. In the analysis of the sensitivity of the selected strains of *M. morganii* registered its sensitivity to cephalosporins, carbapenems, and fluoroquinolones.

Table 1: Frequency of isolated bacterial pathogens isolated from patients with diabetic foot syndrome in different Wagner grades in 2014-2015

Microorganisms	Diabetic foot ulcer in Wagner grades				
	I Grade	II Grade	III Grade	IV Grade	V Grade
<i>Staphylococcus aureus</i>	13	26	27	19	7
<i>Staphylococcus</i> spp.	8	23	33	27	3
<i>Enterococcus</i> spp.	3	14	21	11	2
<i>Escherichia coli</i>	6	11	10	4	4
<i>Citrobacter diversus</i>	4		3	3	
<i>Proteus</i> spp.	2	2	3		3
<i>Enterobacter</i> spp.		2			
<i>Klebsiella pneumoniae</i>				4	5
<i>Morganella morganii</i>		1	1	1	
<i>Pseudomonas aeruginosa</i>		15	13	22	6
<i>Acinetobacter</i> spp.				2	2
<i>Candida</i> spp.		2	2		
Total	36	96	113	95	32

Table 2: Frequency of isolated bacterial pathogens isolated from patients with diabetic foot syndrome in different Wagner grades in 2014-2015

Antibiotics	Frequency of susceptible strains, %			
	II Grade	III Grade	IV Grade	V Grade
Ceftazidime	60	33.3	36.36	0
Cefoperazone	100	75	85.7	50
Cefepime	100	75	54.45	33.3
Meropenem	100	100	85.7	50
Imipenem	100	100	100	100
Ciprofloxacin	60	75	75	50
Levofloxacin	80	100	68.18	50
Amikacin	40	50	42.7	33.3
Netilmicin	80	83.3	85.7	83.3
Gentamicin	60	66.6	57.1	50

In patients with Grade V feet on the degree of destruction Wagner Enterobacteriaceae accounted for 37.5% of the total allocation of pathogens, of which 83.3% of isolates produced beta-lactamase extended spectrum. All isolates of Enterobacteriaceae showed sensitivity to carbapenems and recorded resistance to fluoroquinolones. Sensitivity to aminoglycosides was differed in isolated Enterobacteriaceae. *E. coli* was characterized by resistance to amikacin; strains were *K. pneumoniae* susceptible to amikacin in 50% of cases, *P. vulgaris* in 100% of cases showed its sensitivity to amikacin.

Studying the *P. aeruginosa* sensitivity to antibiotics an increase in resistance level to β -lactams was registered at deep lesions. Thus, the resistance to cefepime reduced from 100% in Grade II to 50% in Grade V, at the same time there revealed a low sensitivity to ceftazidime, which was

60% in Grade II to 0% sensitive strains in V Grade. All isolated strains of *P. aeruginosa* were showed sensitivity to imipenem. Strains, which were isolated in IV and V Grade were resistant to meropenem in 85.7% and 50% cases, respectively.

We revealed a low sensitivity of *P. aeruginosa* to amikacin: From 33.3% to 50% were susceptible to amikacin in patients with DFI. Sensitivity to gentamicin varied from 66.6% susceptible strains in Grade III to 50% susceptible strains in Grade V. It was detected sensitivity to netilmicin, which ranged from 75% to 100%. It was detected low sensitivity to fluoroquinolones: Susceptible strains *P. aeruginosa* to ciprofloxacin, which ranged from 75% to 50%, in III-V Grade. We revealed a reduction in sensitivity to levofloxacin from 80% in Grade II to 50% in Grade V. In comparison with the data by Privolnev 2011, there is an increase in *P. aeruginosa* resistance to cephalosporins, fluoroquinolones, and aminoglycosides, in contrast to, in particular, netilmicin and less amikacin and gentamicin revealed in the studied period.^[14]

The isolated strains of *A. baumannii* in Grade IV and had a high level of resistance to different groups of antibacterial drugs. The isolated strains are resistant to penicillins, cephalosporins, fluoroquinolones, and aminoglycosides. In 100% of cases, the microorganisms are sensitive only to the carbapenems (Table 2). The researchers of Belgorod Regional Clinical Hospital revealed a higher level of resistance of *A. baumannii* as compared with the data of other researchers.^[20]

CONCLUSION

1. The main pathogens in case of foot infections on the background of DM are *S. aureus* (19.2%),

coagulase-negative staphylococci (30.4%), *P. aeruginosa* (14.4%), *E. coli* (6.4%), *Proteus* spp. (4.0%), and *C. diversus* (3.2%) in patients with DFI undergoing inpatient treatment in the Department of Purulent Surgery of St. Joseph Belgorod Regional Clinical Hospital in 2014-2015.

2. It was dominated Gram-positive cocci in Wagner Grade I-III: *S. aureus* was isolated in 36.34-23.89% cases; *Staphylococcus* spp. was detected in 22.22-28.94% cases; *Enterococcus* spp. was determined at 8.33-18.5% cases in Wagner Grade IV and V was found increase amount Gram-negative rods from 39.18% to 63.63%, respectively. It was presented Enterobacteriaceae spp. and *P. aeruginosa*. The analysis of antibiotic susceptibility of Gram-positive strains recorded increase of resistance to oxacillin in isolated strains of *Staphylococcus* spp. (*S. aureus* and coagulase-negative staphylococci) from 25% to 100% in Wagner Grade I and V, respectively. In Wagner Grade IV and V were detected Enterobacteriaceae producing extended spectrum beta-lactamase in 75% (*E. coli*, *K. pneumoniae*, and *C. diversus*) and 83.3% (*E. coli*, *P. vulgaris*, and *K. pneumoniae*) cases, respectively. Studying the *P. aeruginosa* sensitivity to antibiotics in Wagner Grade IV and V was registered decrease susceptibility to ceftazidime in 36.36% and 0%, meropenem in 85.7% and 50%, levofloxacin in 68.18% and 50%, ciprofloxacin in 54.54% and 50%, and amikacin in 42.7% and 33.3%, respectively.
3. For initial antibiotic therapy of foot infections in diabetic patients in the Department of Purulent Surgery of St. Joseph Belgorod Regional Clinical Hospital recommends III generation cephalosporins without activity against *P. aeruginosa*, fluoroquinolones. In patients with Grade III-IV, recommends to use vancomycin, fluoroquinolones, and cefoperazone with further correction of antibiotic therapy based on bacteriological examination of data. In patients with Grade V recommends for Gram-positive flora must be allocated to the use of vancomycin, with Gram-negative flora is possible to use amikacin, with proven sensitivity cefoperazone, cefepime, and fluoroquinolones. Carbapenems, to use as antibacterial therapy for allocating allowance Enterobacteriaceae producing beta-lactamase spread spectrum. When *Pseudomonas* infection as therapy reserve can be used imipenem/cilastatin.

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Source of Support: Nil. **Conflict of Interest:** None declared.