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Original Research

Alternative antibacterial therapy of Methicillin-resistant Staphylococcus aureusin patients with diabetic foot and sepsis

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Abstract

A total of 210 patients with diabetic foot and sepsis who were treated in the purulent-septic center of Zaporizhzhya, Ukraine, were examined for the period of 2007–2020. All patients had type II diabetes mellitus, with a duration of 12.6 ± 2.7 years and an age of 56.8 ± 2.5 years. The diagnosis of sepsis is established according to the criteria of Sepsis-3 (2016). The complex of therapeutic measures included the mandatory use of antibacterial drugs, which was preceded by a microbiological study of biological material (blood and wound discharge). Gram-positive flora was detected in 118 (56.2%) patients and prevailed over gram-negative 81 (38.6%), anaerobes were detected in six (2, 8%) patients, and fungal flora in five (2.4%). Among patients diagnosed with Staphylococcus aureus 52 (100%), Methicillin-resistant Staphylococcus aureus (MRSA) prevailed with 38 (73.0%) ($p < 0.05$). We have identified a pattern that allowed us to categorize patients with MRSA into four groups according to similar sensitivity to antibacterial drugs, which received the conventional designations MRSA type 1; MRSA type 2; MRSA type 3; MRSA type 4. Moreover, MRSA type 4–3 (7, 9%) of the patient is pan-resistant. The most universal drugs in the presence of MRSA in patients with sepsis caused by complicated DFS are daptomycin, linezolid, teicoplanin, vancomycin, and tigecycline. In patients with MRSA type 1 and MRSA type 2, except standard anti - MRSA antibiotics, aminoglycosides, fluoroquinolones and macrolides can be effectively used as first-line drugs.

Keywords: Antibacterial therapy, diabetic foot, Methicillin-resistant Staphylococcus aureus, sepsis.

Introduction

Sepsis remains one of the most urgent and complex medical and social problems due to the stable increase in the number of patients and high mortality. Every year, the incidence of sepsis in the world increases by 8–13%, which requires huge material costs for the treatment of patients of this category [1–3].

It is known that the mortality rate of patients with sepsis depends on the age of the patients, the type of pathogen, the condition of the focus of infection, concomitant pathology, and directed antibiotic therapy (ABT) [4–7].

The existing basic recommendations of the European Concept for the Treatment of Sepsis (Surviving Sepsis Campaign) clearly state that ABT is the most important component of the

comprehensive treatment of sepsis. In recent years, strong evidences have been obtained that timely administration of ABT leads to a decrease in mortality and complication rates (evidence category C) [8–11].

Among the problems associated with ABT, the most significant is the development of resistance to β-lactams in Staphylococcus aureus (S. aureus) and other representatives of gram-positive microflora [12, 13].

The frequent clinical inefficiency of ABT is due to the presence of Methicillin-resistant Staphylococcus aureus (MRSA), which leads to a worsening of the course of the disease and the development of complications [14–16].

S. aureus is an important human pathogen responsible for infectious diseases in the population as well as in healthcare facilities. The adaptive ability of S. aureus to antibiotics led in the early 1960s to the appearance of methicillin-resistant Staphylococcus aureus (MRSA). The cause of resistance to methicillin and all other beta-lactam antibiotics is themecAgene, which is located in the mobile genetic element, the staphylococcal cassette chromosome mec (SCCmec) (mobile genetic element, the staphylococcal cassette chromosome mec (SCCmec)) [17–19].

Studies comparing active screening for identification of MRSA carriers upon admission to the hospital (using the rapid molecular test or standard blood culture method) or the lack of screening have shown that the diagnosis of MRSA followed by eradication is a major factor in increasing patient survival by sepsis [20–22].

S. aureus can easily become antibiotic resistant, and MRSA is multidrug resistant. MRSA is a serious problem, as it leads to an increase in mortality, despite the use of expensive antibiotics as a last resource [23–26].

The resistance to vancomycin, the main traditional anti-MRSA antibiotic, is rare, although isolates with reduced sensitivity are found in many regions. Linezolid and daptomycin remain largely active against the vast majority of MSSA and MRSA [27].

Since S. aureus is constantly evolving, it is important to monitor the epidemiology of its various strains, since information at the regional level will help in forming a global perspective [28–30].

Materials and Methods

A total of 210 patients with sepsis, the cause of which was complicated diabetic foot syndrome (DFS) were examined. Patients were treated in the purulent-septic city center of Zaporizhia, for the period of 2007–2020. All patients had type 2 diabetes mellitus (T2DM), the average duration of which was 12.6 ± 2.7 years. The average age of the patients was 56.8 ± 2.5 years.

The diagnosis of sepsis is made according to the criteria set out in the International Guidelines for the treatment of sepsis and septic shock -Sepsis-3 (2016), using the Quick SOFA scale. Thus, after the diagnosis of sepsis was determined, the patients were transferred to the high-risk group and continued treatment in the intensive care unit.

The reason for the development of sepsis was a purulent-necrotic lesion of the foot – an abscess, phlegmon, purulent tendovaginitis, purulent arthritis, gangrene.

According to the classification of the International Working Group on Diabetic Foot Problems (1991), patients were divided into clinical forms – 86 patients with a neuropathic form of DFS and 124 – with a mixed one. According to the WIFI classification (2014), patients had a characteristic of 2(3)0(1)3. The local reaction was characterized by signs of inflammation: purulent discharge, redness of the skin, pain, swelling, local hyperthermia, lymphangitis. Fascia, muscles, tendons, and bones of the foot were involved in the pathological process.

Perfusion of the lower extremities was characterized by moderate impairment of the main and microcirculatory blood flow, the ankle-brachial index (ABI) was recorded in the range of 0.6–0.9. The indicator of the transcutaneous oxygen tension at the foot (TcPO2) was ≥60 mm Hg. Art. All patients had diabetic neuropathy of varying severity.

All patients were operated on, and the complex of therapeutic measures included the mandatory use of antibacterial drugs, which was preceded by a microbiological study of biological material (blood and wound discharge). The qualitative composition of the flora and the sensitivity of the

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isolated cultures to antibiotics were determined using BacT/ALERT media to isolate microorganisms using a Vitek 2 Compact automatic bacteriological analyzer (Biomerieux, France). The technical capabilities of the method allow identification of aerobic and facultative anaerobic microorganisms, except non-spore-forming anaerobic microorganisms, as well as discovering the presence of MRSA. The study was conducted during hospitalization and in dynamics.

Statistical analysis was performed using descriptive statistics. Checking the data for the normality of the distribution was carried out visually by the histogram and using the Kolmogorov-Smirnov test. Given the normal distribution in the analyzed samples, the parameters of the parametric descriptive statistics were calculated in the format M ± m (average value ± standard error of the average value). The significance of differences was evaluated depending on the analyzed data using the Student's parametric criterion. Differences were considered significant at $p < 0.05$.

Results

Primary antibiograms of 210 patients with sepsis made it possible to determine the pathogen and its sensitivity to antibacterial drugs (table 1).

Gram-positive flora was detected in 118 (56.2%) patients and prevailed over gram-negative - 81 (38.6%), anaerobes were detected in 6 (2, 8%) patients, and fungal flora in 5 (2.4%).

The leaders among the pathogens were Staphylococcus aureus – 52 (24.7%), Enterococcus faecalis – 29 (13.8%), Pseudomonas aeruginosa – 23 (10.9%), Staphylococcus epidermidis – 16 (7.6%), Escherichia coli – 15 (7, 1%), Acinetobacter baumannii – 13 (6.2%), the remaining bacteria was less than 5%.

Patients diagnosed with *Staphylococcus Aureus* 52 (100%) are differentiated by the presence of the Methicillin-resistant Staphylococcus aureus gene (MRSA): detected in 38 (73.0%), absent in 14 (27.0%). The amount of MRSA was significantly ($p<0.05$) greater than Methicillin-sensitive Staphylococcus aureus (MSSA).

The pathogen type and invitro sensitivity to known antibiotic groups was studied standardly: β-lactams, aminoglycosides, fluoroquinolones, macrolides, lincosamides, lipopeptides, oxazolidinones, glycopeptides, sulfanilamide's, tetracyclines, rifampicin (table).

Among the patients with MSSA 14 (100%), 13 (92.8%) of them had predicted resistance to ceftazidime. Resistance to cephalosporins of the 1st and 2nd generation was revealed in 6 (42.8%) patients, to natural and semi-synthetic penicillin's – in 12 (85.7%) patients. To protected penicillin's, 3rd and 4th generation cephalosporins, carbapenems – no resistance was detected. The phenotype of resistance to tobramycin from the aminoglycoside group was noted in 100% of patients. A resistance level of more than 50% was detected for drugs from the macrolide group, lincosamides lipopeptides, ciprofloxacin and levofloxacin from the fluoroquinolone group.

The sensitivity level of more than 92% was found in: amikacin, gentamicin, netilmicin (aminoglycoside group), and moxifloxacin (group of fluoroquinolones). In vancomycin, teicoplanin (group of glycopeptides), the sensitivity level is up to 80%.

No phenotype of resistance was detected in linezolid (group of oxazolidinones), trimethoprim / sulfamethoxazole (group of sulfonamides), and all drugs from the group of tetracyclines.

According to the data obtained, MSSA is sensitive to varying degrees: protected aminopenicillins; 3rd generation cephalosporins (ceftriaxone); 3rd generation protected cephalosporins; 4th generation cephalosporins (cefepime); preparations from the aminoglycoside group (except tobramycin); fluoroquinolones; lincosamides; glycopeptides; tetracyclines; sulfonamides (trimethoprim/sulfamethoxazole).

A study of the resistance of Staphylococcus aureus in the presence of the MRSA gene in 38 (100%) patients confirmed its genetic 100% resistance to all β-lactams. A resistance level of up to 50% was found for kamikacin, gentamicin, netilmicin (a group of aminoglycosides). Drugs from the group of fluoroquinolones, macrolides, sulfonamides – sensitivity level up to 30%.

When processing data on the resistance of MRSA, a pattern was revealed that allowed us to categorize patients into four groups that were

Table 1: The sensitivity of *Staphylococcus Aureus* to antibiotics in patients with diabetic foot and sepsis.

Antibiotics in groups	MSSA	MRSA type 1	MRSA type 2	MRSA type 3	MRSA type 4
β-lactam antibiotics		0	0	0	0
benzylpenicillin	0/1	0	0	0	0
Ampicillin	0/1	0	0	0	0
amoxicillin	0/1	0	0	0	0
Ticarcillin	0/1	0	0	0	0
piperacillin	0/1	0	0	0	0
ampicillin-sulbactam	1	0	0	0	0
amoxicillin-clavulanate	1	0	0	0	0
ticarcillin-clavulanate	1	0	0	0	0
piperacillin-tazobactam	1	0	0	0	0
Cefazolin	0/1	0	0	0	0
cefuroxime	0/1	0	0	0	0
ceftriaxone	1	0	0	0	0
ceftazidime	0	0	0	0	0
Cefepime	1	0	0	0	0
ceftriaxone-tazobactam	1	0	0	0	0
ertapenem	1	0	0	0	0
imipenem/cilastatin	1	0	0	0	0
meropenem	1	0	0	0	0
Aminoglycosides					
Amikacin	1	1	1	0	0
gentamicin	1	1	1	0	0
Netilmicin	1	1	1	0	0
tobramycin	0	0	0	0	0
Quinolones/Fluoroquinolones					
ciprofloxacin	0/1	1	0	0	0
levofloxacin	0/1	1	0	0	0
moxifloxacin	1	1	0	0	0
Macrolides					
azithromycin	0/1	1	0	0	0
clarithromycin	0/1	1	0	0	0
roxithromycin	0/1	1	0	0	0
Lincosamides					
clindamycin	0/1	0	0	0	0
lincomycin	0/1	0	0	0	0
Lipopeptides					
daptomycin	0/1	1	1	1	0
Oxazolidinones					
Linezolid	1	1	1	1	0

(*continues*)

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Table 1: *Continued*

Antibioticsingroups	MSSA	MRSA type 1	MRSA type 2	MRSA type 3	MRSA type 4
Glycopeptides					
vancomycin	0/1	1	1	1	0
teicoplanin	0/1	1	1	1	0
Tetracyclines					
tetracycline	1	0	0	0	0
doxycycline	1	0	0	0	0
minocycline	1	0	0	0	0
tetracycline	1	0	0	0	0
tigecycline	**1**	**1**	**1**	**1**	**0**
Sulfonamides					
trimethoprim/sulfamethoxazole	1	1	1	0	0
Rifamycins					
rifampicin	0	0	0	0	0

Note.0 - no sensitivity; 1 - sensitive; 0/1 - sensitivity 40–80%; the regularity for this group is highlighted in color.

designated: MRSA type 1; MRSA type 2; MRSA type 3; MRSA type 4.

In MRSA type 1, 10 (26.3%) patients, sensitivity to aminoglycosides (amikacin, gentamicin, netilmicin), fluoroquinolones (ciprofloxacin, levofloxacin, moxifloxacin), macrolides (azithromycin, clarithromycin, clarithromycin, linklinkin), lipopeptides (daptomycin), oxazolidinones (linezolid), glycopeptides (vancomycin, teicoplanin), tetracyclines (tigecycline), sulfonamides (trimethoprim/sulfamethoxazole) are preserved.

MRSA type 2, 9 (23.7%) patients, was characterized by sensitivity to aminoglycosides (amikacin, gentamicin, netilmicin), lycopeptides (daptomycin), oxazolidinones (linezolid), glycopeptides (vancomycin, teicoplanin), tetracyclines (taigetracycline, (trimethoprim/sulfamethoxazole).

MRSA type 3, 16 (42.1%) patients were sensitive to lycopeptides (daptomycin), oxazolidinones (linezolid), glycopeptides (vancomycin, teicoplanin), tetracyclines (tigecycline).

MRSA type 4, 3 (7.9%) patients were pan-resistant.

Discussion

A screening study of blood in patients with sepsis allows to determine the qualitative composition of the flora, sensitivity to antibiotics, and to identify multiresistant and pan-resistant strains. To conduct effective antibiotic therapy it is currently not enough to identify the pathogen, it is important to determine the presence of the phenotype of resistance to various drugs.

Possibly a specific genetic variant of MRSA corresponds to its portrait of antibacterial resistance and sensitivity, with common features, but noticeable differences.

The most effective drugs in the presence of MRSA, in 35 (92.1%) patients, are identified: tigecycline (group of tetracyclines), daptomycin (a group of lycopeptides), linezolid (oxazolidinones), teicoplanin, vancomycin (a group of glycopeptides).

Thus, in some patients with MRSA 19 (50%) type 1 and type 2, in addition to standard anti - MRSA antibiotics, aminoglycosides, fluoroquinolones, and macrolides can also be effective.

Conclusion

1. A blood screening study in patients with sepsis caused by complicated DFS has allowed us to determine the qualitative composition of the flora, sensitivity to antibiotics, and to identify multiresistant and pan-resistant strains.

2. In the group of patients with sepsis and with diagnosed Staphylococcus aureus, MRSA gene was detected in 38 (73.0%) patients; its number was significantly ($p<0.05$) higher than MSSA.
3. The most universal drugs in the presence of MRSA in patients with sepsis caused by complicated DFS are: daptomycin (a group of lycopeptides), linezolid (oxazolidinones), teicoplanin, vancomycin (a group of glycopeptides), and tigecycline (a group of tetracyclines).
4. In some patients with MRSA, depending on the genetic variant (up to 50%), in addition to standard anti-MRSA antibiotics, aminoglycosides, fluoroquinolones, and macrolides can also be effective.
5. The different genetic variant of MRSA corresponds to its portrait of antibacterial resistance and sensitivity, with common features, but noticeable differences.

Conflict of Interest

The authors declare no conflict of interest.

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