DIAGNOSTIC AND TREATMENT METHODS

V.S. Gorokhovskii, Y.A. Zhuravlev, E.G. Kovaleva,
N.A. Nevskaia, S.V. Diachenko, E.V. Slobodeniuk

DYNAMICS OF THE RESISTANCE TO ANTIMICROBIAL DRUGS IN THE MULTIDISCIPLINARY SURGICAL HOSPITAL FROM 2006 TO 2016

ABSTRACT

The analysis of the structure and resistance to antimicrobial agents of purulent-inflammatory disease pathogens in patients in a multidisciplinary surgical hospital has been carried out. It was revealed that *Escherichia coli, Klebsiella pneumonia, Klebsiella oxytoca* are leading in the structure of pathogens of purulent-inflammatory diseases. The statistical forecast assumes a further increase in the proportion of microorganisms of the *Enterobacteriaceae* family and an increase in the proportion of pan-resistant strains of *Klebsiella pneumonia*. According to the results of microbiological monitoring, it is necessary to use protected aminopenicillins and levofloxacin as the starting empirical therapy for the treatment of infections caused by *E. coli,* and for *K. oxytoca, Kl. pneumonia* - levofloxacin, IV generation cephalosporins and carbapenems.

Keywords: microbiological monitoring, antimicrobial drugs.

Introduction. Purulent-septic diseases occupy one of the leading positions in the morbidity structure in the multidisciplinary surgical hospital. Number of patients with purulent-septic diseases is about one-third of all surgical patients. The modern range of surgical treatments (abdominal and thoracic surgery, bones and joints, vessels, etc.) create the danger of suppuration of postoperative wounds, which often leads to direct threat to patients' lives. More than half of all deaths after surgery are associated with the development of infectious complications.

Treatment of purulent-septic diseases is multipurpose and necessarily includes the use of antimicrobial drugs.

Discovery of antibiotics in the XX century leads to a significant decrease in severity and mortality from purulent-septic diseases. However, in recent years, the growth of microorganisms' resistance to antibiotics has become an urgent public health problem [2]. Its' importance is determined by the fact that antimicrobial resistance affects many aspects. The spread of resistant microorganisms in hospitals leads to an increase of hospitalization, treatment costs, and lethality, especially in high-tech interventions (heart surgery, transplantation, oncohematology) [1].

The economic importance of antibiotic resistance is determined by compulsory usage of antibiotics with wider spectrum, which cost higher than the traditional drugs for treating infections caused by sensitive microorganisms. The social aspect is determined by the increase of population morbidity, disability, and by the need of using more expensive drugs.

The data of microorganisms' resistance to antibiotics in specific hospital is unique, because there are significant differences in consumption of antibiotics, implementation of medical care standards, and use of the infection control programs in different hospitals. Regarding to the above, there is a need to conduct a local monitoring of antibiotic resistance to optimize the pharmacotherapy for patients with purulent-septic diseases [5].

Aim of the research. To analyze the structure and resistance to antibiotics of purulent-septic diseases pathogens and determine exact treatment for primary empirical antibacterial therapy.

Research problems

1. To analyze dynamics of causes' structure of purulent-septic diseases in the multidisciplinary surgical hospital.

2. Determine the indicators of resistance to antibiotics.

3. Construct a short-term mathematical prognosis about the dynamics of purulent-septic diseases etiology to improve the effectiveness of primary empirical antibacterial therapy.

Research materials and methods. A retrospective complete copy of effective research from the journals of the bacteriological laboratory was taken during the period from 2006 to 2016. (2006. n = 610, 2009. n = 504, 2012. n = 476, 2014. n = 468, 2016. n = 748) about the identification of pathogens and their antibacterial resistance indicators obtained from patients undergoing treatment in a multidisciplinary surgical hospital. Identification of bacteria was carried out according to the documents which regulate the work of bacteriological laboratories. Determination of the of microorganisms' sensitivity to antibiotics was made using the disk-diffusion method. Interpretation of sensitivity indicators was done according to the clinical recommendations "Determination of microorganisms' sensitivity to antibiotics" (approved at the 16th International Congress on Antibiotical Chemotherapy MAKMAX / ESCMID, 21-23 May 2014, Moscow) [3]. Clinical Hospital №10 in Khabarovsk is a modern well-equipped multi-specialized clinic. The hospital is represented by departments of surgical and therapeutic profile. The hospital bed capacity is more than 450 beds, the main type of emergency care provided is surgical, the number of bed - days spent by patients is more than 150 thousand per year, about 15 thousand patients are hospitalized annually. The statistical analysis of the results was counted using descriptive statistics methods in MS Office EX-CEL 2003 and the $\chi 2$ method. The significant differences level was taken as $p < 0.05$.

Results and discussion. Analysis of etiological agents causing purulent-septic diseases in the Clinical Hospital №10 over 10 years showed an increase in the proportion of gram-negative microorgan-

isms of the *Enterobacteriaceae* family, which summary composed over 50% in 2016 (Fig. 1).

With the construction of a prognosis until 2020, further increase in the proportion of microorganisms of Enterobacteriaceae family was expected. Whereas it's going to be a decrease in the proportion of gram-positive microorganisms (p <0.05). At the same time, the relative low proportion of non-enzyme-forming gram-negative microorganisms attracts attention.

Among the microorganisms of the *Enterobacteriaceae* family *Escherichia coli, Klebsiella pneumonia, Klebsiella oxytoca* occupy leading positions (Pic. 2). The proportion *of Escherichia coli* in 2006 was 17.2%, and in 2016 increased to 22.5% (p> 0.05), *Klebsiella pneumonia* 6.1% and 22.6% (p <0.05), *Klebsiella oxytoca* 3.6% and 5.5% (p> 0, 05) respectively.

The most significant increase was observed in *Klebsiella pneumonia*. The proportion of which rised by more than 4 times during the studied time period.

Number of *Proteus mirabilis* and *Proteus vulgaris* (p> 0.05) remains almost unchanged.

Number of *Pseudomonas aeruginosae* also remains unchanged. Showed 1.6% (n = 10) in 2006, and 1.9% (n = 14) in 2016 (p> 0.05).

Among gram-positive microorganisms, there was a significant decrease in the number of *Staphylococcus epidermidis* from 38.4% to 8.2% (p <0.05) over the studied period. A similar situation is observed with *Staphylococcus aureus*. Its' number showed a tendency to fall from 22.5% to 19.9% (p> 0.05).

Indicators of *E. coli* resistance to antibiotics (2006-2016) demonstrate high levels of resistance to the β-lactam group. As for aminopenicillins this indicator is numbered 100% in 2016. For cephalosporins of the third generation there was an increase in resistance indices for cefotaxime from 32.4% in 2006 to 73.2% in 2016 (p <0.05), and for ceftazidime from 54.0% in 2009 to 60.7% in 2016 (p> 0.05) (Table 1). Attention is paid to the persistent low rates of resistance to protected penicillins, which showed 25.5% in 2009. and 19.0% in 2016 (p> 0.05), which is probably due to the extended spectrum of β-lactamase production by *E. coli*, in which there

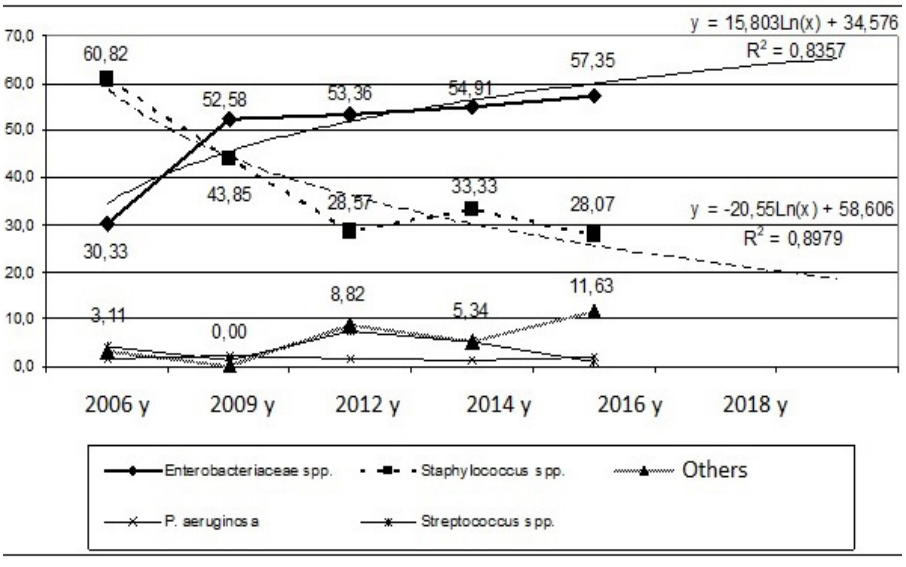

Fig. 1. Structure of microorganisms, selected in samples in 2006 – 2016, predicted to 2020

is a resistance to cephalosporins of I-IV generations and sensitivity to protected aminopenicillins remains [4]. At the same time, over 10 years, a decrease in *E. coli* resistance to fluoroquinolones for ciprofloxacin was noted from 73.3% in 2006 to 19.0% in 2016 (p <0.05) and levofloxacin from 87.6% in 2006 to 20.8% in 2016 (p <0.05). Low levels of resistance in *E. coli* are noted for meropenem 4.7% and amikacin 10.7% in 2016.

In 2006-2016 *Klebsiella oxytoca* showed high levels of resistance to the group of β-lactam antibiotics: for aminopinicillin in 2016 this indicator amounted to 100%, for cephalosporins of the third generation an increase in resistance indices was observed to cefotaxime from 13.6% in 2006 to 78.05% in 2016 (p <0.05) and to ceftazidime from 18.2% in 2006 to 61% in 2016 (p <0.05) (Table 1). The level of *Klebsiella oxytoca* resistance to protected aminopenicillins dynamically increased from 0% in 2006 to 48.8% in 2016 (p <0.05), which is fundamentally different from *E. Coli*. Perhaps, it is an indicator of the *Klebsiella oxytoca* production of gram-negative bacteria chromosomal β-lactamase class C. During the research period there was a decrease in *Klebsiella oxytoca* resistance to ciprofloxacin from 81.8% in 2006 to 31.7% in 2016 (p <0.05) and the increase in resistance to levofloxacin from 22.7% in 2006 to 31.7% in 2016 (p> 0.05). In 2016 low levels of resistance among *Klebsiella oxytoca* was noted only to meropenem 7.3%.

In 2006-2016 similar indicators of resistance also noted among *Klebsiella pneumonia*. An increase in resistance percentage was shown for cefotaxime from 51.4% in 2006 to 75.0% in 2016 (p> 0.05), ceftazidime from 51.4% in 2006 to 68.0% in 2016 (p> 0.05), amikacin from 0% in 2006 to 45.0% in 2016 (p <0.05), to

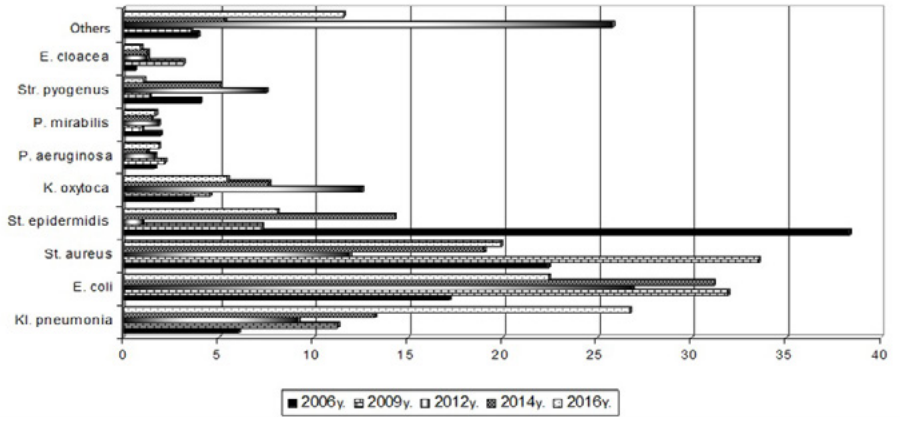

Fig. 2. The etiological causes' structure of the purulent-septic diseases in the multidisciplinary surgical hospital, 2006 – 2016, %

Table 1

The resistance of *E. Coli, Klebsiella oxytoca* and *Klebsiella pneumonia* to antibiotics in the multidisciplinary surgical hospital in a multidisciplinary surgical hospital 2006-2016, %

Antibiotic	*E. coli*					*K. oxytoca*					*K. pneumonia*				
	2006	2009	2012	2014	2016	2006	2009	2012	2014	2016	2006	2009	2012	2014	2016
	n=105	n=161	n=128	n=146	n=168	n=22	n=23	n=60	n=36	n=41	n=37	n=57	n=44	n=62	n=200
Ampicillinum	100.00	97.52	92.19	95.21	100.00	4.55	100.00	100.00	88.89	100.00	100.00	100.00	100.00	98.39	100.00
Amoxillinum/clav. acid	-	25.47	27.34	15.75	19.05	0.00	17.39	6.67	16.67	48.78	48.65	45.61	43.18	38.71	53.50
Cefuroximum	-	-	44.53	67.81	-	-	-	43.33	61.11	-	-	-	43.18	82.26	100.00
Cefotaximum	32.38	45.34	67.97	58.90	73.21	13.64	13.04	50.00	47.22	78.05	51.35	63.16	34.09	72.58	75.00
Ceftazidime	-	54.04	38.28	52.74	60.71	18.18	21.74	50.00	52.78	60.98	51.35	50.88	20.45	61.29	68.00
Cefepimum	-	0.00	22.66	37.67	51.79	-	-	16.67	38.89	51.22	-	-	13.64	37.10	62.50
Meropernem	-	16.15	4.69	1.37	4.76	-	13.04	6.67	0.00	7.32	-	19.30	11.36	9.68	29.00
Ciprofloxacinum	73.33	57.14	82.81	25.34	19.05	81.82	73.91	75.00	61.11	31.71	81.08	68.42	70.45	51.61	51.50
Levofloxacinum	87.62	53.42	57.03	33.56	20.83	22.73	34.78	73.33	41.67	31.71	94.59	78.95	63.64	46.77	49.00
Amicacinum	0.00	34.16	45.31	35.62	10.71	27.27	43.48	56.67	55.56	29.27	0.00	59.65	43.18	29.03	45.00
Doxycuclinum	8.57	20.50	67.19	41.78	62.50	36.36	39.13	46.67	30.56	63.41	45.95	40.35	45.45	38.71	95.50

Meropenem from 19.3% in 2009 to 29.0% in 2016 (p> 0.05). Negative predictive occasion for a medical organization is the identification of pan-resistant strains (PDR (pandrug resistance) - resistance of microorganisms to all antibiotics) *Klebsiella pneumonia*. For the first time, pan-resistant strains of *Klebsiella pneumonia* were detected in 2014 (among three patients) - 4.8%, but already in 2016 these strains were seen already among 46 patients - 23% (p <0.05).

More adavantageous situation with levels of resistance to antibiotics is noted in *Staphylococcus aureus*. Despite the increase in the number of oxacillin-resistant strains of *Staphylococcus aureus* (MRSA) from 0.7% in 2006 to 39.6% in 2016 (p <0.05), only one vancomycin-resistant strain was detected in 2016.

Conclusions

1. The main position in the cause structure of purulent-septic diseases is occupied by *Escherichia coli, Klebsiella pneumoniae, Klebsiella oxytoca, Staphylococcus aureus*.

2. Predictively the increase in density of *Enterobacteriaceae* family and panresistants straines of *Klebsiella pneumonia* is expected.

3. The sensitivity of strains of *Staphylococcus aureus* demonstrates a high number of oxacillin-resistant strains (MRSA).

4. According to the results of microbiological monitoring protected aminocillin and levofloxacin should be used as the primary starting therapy for *E. coli* and levofloxacin, cefalosporins IV generation and carbapenem should be used for *Kl. oxytoca, Kl. Pneumonia*.

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Information about authors:

st. Muravyev-Amurskii, 35, 204, Khabarovsk Territory, Khabarovsk, 680000, Russian Federation:

Gorokhovskii Vadim Semenovich, Head of the Department of Anesthesiology-Resuscitation, Transfusiology and Emergency Medical Aid, FESMU, Associate Professor, Ph.D., vadsgor@yandex.ru;

Zhuravlev Yaroslav Aleksandrovich, Head of the Infec-

Table 2

The resistance of *St.aureus* to antibiotics in the multidisciplinary surgical hospital in a multidisciplinary surgical hospital 2006-2016, %

Antibiotic	*S. aures*				
	2006	2009	2012	2014	2016
	n=137	n=169	n=57	n=89	n=149
Ciprofloxacinum	6.6	39.6	70.2	69.7	35.6
Levofloxacinum	2.9	34.9	42.1	62.9	34.2
Amicacinum	13.1	68.0	70.2	75.3	36.9
Doxycuclinum	8.8	16.0	22.8	69.7	40.9
Lincomycinum	89.1	87.0	59.6	60.7	34.9
Erythromycinum	100.0	68.6	84.2	87.6	41.6
Oxacillinum	0.7	39.1	54.4	68.5	39.6
Vancomycinum	0.0	0.0	0.0	3.4	0.7
Linezolidum	-	-	0.0	0.0	0.0

tious Diseases Department of the «City Hospital №10» of the Ministry of Health of the Central Committee, Associate Professor of the Department of Infectious Diseases, FESMU, Ph.D. suba-rus@mail.ru;

Nevskaia Nina Alexandrovna, Assistant of the Department of Anesthesiology-Resuscitation, Transfusiology and Emergency Medical Aid, FSBEI HE FGMU Ministry of Health of the Russian Federation, newskayan@rambler.ru;

Kovaleva Evgeniia Gennadevna, TB specialist, "Tuberculosis Hospital", Khabarovsk, eva.kovaleva.25@inbox.ru;

Diachenko Sergei Vladimirovich, Professor of the Department of Pharmacy and Pharmacology, FESMU, Dr. med., stenotrophomonas@yandex.ru;

Slobodeniuk Elena Vladimirovna, Head of the Department of Pharmacy and Pharmacology FESMU, Professor, Doctor of Biology, helena_slobodenuk@mail.ru.

E.V. Fomichev, L. D. Weisheim, M. V. Kirpichnikov, E. N. Yarygina, A.V. Mikhalchenko, A.V. Yurkevich, I.D.Ushnitsky

THE DIAGNOSTCS AND TREATMENT OF ENDOGENOUS INTOXICATION IN PATIENTS WITH MANDIBLE TRAUMATIC OSTEOMYELITIS

ABSTRACT

Quite often standard methods of treatment of traumatic osteomyelitis of the lower jaw do not lead to a suppression of the purulent-inflammatory process in the bone tissue and the disease acquires a lukewarm torpid nature of the flow with periodic exacerbations. An important task of clinical medicine is to determine the presence and assessment of the severity of endogenous intoxication. For diagnostics, it is usually proposed to determine the level of endotoxic substances and parameters of the cellular composition of the blood, special indexes of intoxication are calculated for facilitating the interpretation of these changes in populations and subpopulations of blood cells, but a sufficient evidence base to facilitate the interpretation of laboratory data is not yet formed.

The **aim** of the study was to determine the diagnostic efficiency of laboratory parameters in endotoxicosis caused by traumatic osteomyelitis of the lower jaw, as well as the development of a diagnostic algorithm and complex treatment depending on the stage of chronic endogenous intoxication. Patients with traumatic osteomyelitis of the lower jaw at the age of 18 to 65 years were examined. In addition to the traditional clinical and laboratory examination, an assessment of the nature and severity of chronic endogenous intoxication was carried out using the developed test suite.

As a result of the study, it was found that the most informative in the prognostic plan is the definition of the level of "medium-mass molecules", diene conjugates and the sorption capacity of erythrocytes. Other parameters investigated, including integral leukocyte indices of intoxication, are inferior to them for diagnostic value. Analysis of the results of clinical and laboratory studies shows the important role of chronic endogenous intoxication in the imbalance of homeostasis systems that caused atypical or torpid manifestations of the disease. The results of the study showed that the most informative methods for detecting the presence and subsequent dynamic monitoring of the level of endogenous intoxication should be recognized as the definition of sorption capacity erythrocytes and the level of "medium-mass molecules". Integral leukocyte indices of intoxication can be used to identify patients at risk of a complicated course of the disease, who need an in-depth biochemical examination.

Keywords: traumatic osteomyelitis, sorption capacity of erythrocytes, leukocyte indices of intoxication, endotoxicosis.

Introduction. Increasing the effectiveness of treatment of traumatic osteomyelitis of the lower jaw (TOLJ) continues to be one of the urgent problems of maxillofacial surgery. Quite often the standard methods of treatment do not lead to the suppression of the purulent-inflammatory process in the bone tissue and the disease acquires a torpid nature of the flow with periodic exacerbations [1, 2, 5].

Long-term presence of microorganisms and their toxins in the bloodstream, accumulation of under-oxidized metabolic products lead to the development of chronic metabolic stress of the patients' body. Endogenous intoxication is extremely important, and with a certain phase of the disease it becomes a leading pathogenetic element of many chronic inflammatory diseases of the maxillofacial region. According to the definition, endotoxicosis is a complicated autocatalytic process that eventually acquires a universal character,that less and less depends on the mechanisms that triggered it. During an endotoxicosis unbalanced biologically active substances are becoming aggressive agents. The term of "endogenous toxic substances" means substances of biological origin, which accumulating in the body above the normal level, have a damaging effect on organs and systems [3]. In this case, the basic systems of biotransformation and toxic substances get unbalanced, that lead to the development of