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MONITORING OF THE DYNAMICS OF ANTIMICROBIAL RESISTANCE AMONG WOUNDED IN THE CONDITIONS OF ARMED CONFLICT

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Introduction. *The article presents the results of monitoring antibiotic resistance of microorganisms isolated from military personnel undergoing long-term treatment in specialized hospitals. A high level of resistance to antibacterial drugs was established. The predominance of gram-negative microflora was noted not only in the general structure of the development of purulent-inflammatory processes, but also in resistance. Of particular concern are isolates that have proven to be resistant to the reserve group of drugs.*

Purpose. *Monitoring the sensitivity of microorganisms to antibacterial drugs in patients with various types of injuries caused by military events.*

Materials and methods. *Bacteriological examination of biological material using Vitek-2 Biomerieux automated pathogen systems and classic, followed by determination of sensitivity using the disk-diffusion method.*

Results. *Mine-explosive injuries of a severe degree and bullet wounds are the main ones in the structure of combat casualties among the hospitalized. Antibiotics and antimicrobials play a crucial role in reducing morbidity and mortality, and not only among humans. The danger is caused by injured persons with penetrating wounds and persons with surgical intervention, open multifragmentary fractures, endoprosthetics, metal implants and burns. During the bacteriological examination, 439 types of microorganisms were isolated, 38.4% of which were MRSA, vancomycin-resistant enterococci, colistin-resistant and carbopenem-resistant gram-negative rods. Also, 24.0% were isolated MDR strains (resistant to two or more groups of antibiotics). There was a quantitative predominance of Gr(-) flora over Gr(+). Today, antibiotic resistance is increasing to significant levels throughout the world. In addition to the mechanisms already familiar to us, new ones are being formed that contribute to the development of unpredictable situations during treatment. Timely started treatment makes it possible to control the course of the infectious process and increases the chances of the patient's recovery. In this case, the time factor plays a key role.*

Conclusions. *During the analysis of antibiotic resistance of microorganisms, an increase in the level of resistance of almost all groups of isolates was found. The levels and spectra of antibiotic resistance in relation to widely used antibacterial drugs were determined. Comparative results of bacteriological examinations of patients for 2022 and 2023. allow us to draw a conclusion about the high level of circulation of polyresistant clinical isolates. In monitoring patients, in 2023, drugs of the reserve group were used 1.8 times more often than in the period of 2022. which indicates a growing resistance to the main medicines. The obtained data make it possible to detect the formation of hospital strains in a timely manner, to carry out epidemiological analysis and effective management. Thanks to the joint work of the military and civilian health care systems, 70% of military personnel are able to return to the ranks of defenders.*

Key words: *mine-blast injuries, antibiotic resistance, antibiotics, drug resistance.*

МОНІТОРИНГ ДИНАМІКИ РЕЗИСТЕНТНОСТІ МІКРООРГАНІЗМІВ ПОРАНЕНИХ ВІЙСЬКОВОСЛУЖБОВЦІВ В УМОВАХ ВІЙСЬКОВОГО КОНФЛІКТУ

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Вступ. *У статті представлені результати моніторингу антибіотикорезистентності мікроорганізмів, ізольованих у військовослужбовців, що перебували на тривалому лікуванні в межах спеціалізованих стаціонарів України. Встановлено високий рівень стійкості до антибактеріальних препаратів. Відмічено превалювання грамнегативної мікрофлори не тільки у загальній структурі розвитку гнійно-запальних процесів, а і у резистентності до лікарських засобів. Особливе занепокоєння викликають ізоляти, що виявились стійкими до резервної групи лікарських засобів.*

Мета. *Проведення моніторингу чутливості мікроорганізмів до антибактеріальних препаратів у поранених військовослужбовців з різними видами травм, причиною яких стали військові дії.*

Матеріали та методи. *Бактеріологічне дослідження біологічного матеріалу проводили на автоматизованих системах індикації патогенів Vitek-2 Biomerieux і класичним бактеріологічним, з подальшим визначенням чутливості диско-дифузійним методом.*

Результати. *Мінно-вибухові травми тяжкого ступеню та кульові поранення є основними у структурі бойових втрат серед госпіталізованих. Антибіотики та протимікробні препарати відіграють вирішальну роль у подоланні рівня захворюваності і смертності серед поранених після тяжких комбінованих травм в умовах сучасних бойових конфліктів. Небезпеку викликають травмовані з наскрізними пораненнями та особи з хірургічним втручанням, відкритими багатоуламковими переломами, ендопротезуванням, металевими імплантами та опіками. При проведенні бактеріологічного дослідження було виділено 439 видів мікроорганізмів з 298 зразків біологічного матеріалу. З яких 38,4% складали метицилін-резистентні штами S. aureus (MRSA), ванкоміцин-резистентні ентерококи, колістин-резистентні та карбопенем стійкі грамнегативні палички. Також 24,0% були виділені штами MDR (резистентні до двох і більше груп антибіотиків). Наявним було кількісне переважання Грамм(-) флори над Грамм(+). З впевненістю можна стверджувати, що антибіотикорезистентність зростає до значних рівнів в усьому світі. Окрім знайомих уже нам механізмів, формуються нові, які сприяють розвитку непередбачуваних ситуацій при лікуванні. Своєчасно розпочате лікування дає змогу контролювати перебіг інфекційного процесу і підвищує шанси на одужання пацієнта. Фактор часу при цьому відіграє ключову роль.*

Висновки. *При проведенні аналізу антибіотикорезистентності виділених мікроорганізмів, виявлено підвищення рівня стійкості практично усіх груп ізолятів. Визначено рівні і спектри антибіотикорезистентності по відношенню до широкозастосовуваних антибактеріальних препаратів. Порівняльні результати бактеріологічних досліджень хворих за 2022 та 2023рр. дозволяють зробити висновок про високий рівень циркуляції полірезистентних клінічних ізолятів. У моніторингових хворих у 2023р. препарати групи резерву використовували у 1,8 разів частіше, ніж за період 2022р. що свідчить про зростаючу стійкість до основних лікарських засобів. Отримані дані дозволяють своєчасно виявляти формування госпітальних штамів, проводити епідеміологічний аналіз та ефективне управління. Завдяки спільній праці військової та цивільної систем охорони здоров'я, у майже 70% випадків поранень, військовослужбовці повертаються у лави захисників.*

Ключові слова: *мінно-вибухові травми, вогнепально-кульові ушкодження, осколкові поранення, компресійно-здавлені травми (КЗТ), синдром травматичного ендотоксикозу (СТЕ), антибіотикорезистентність, антибіотики, стійкість до лікарських засобів.*

Introduction. The problem of antibiotic resistance of microorganisms is always a matter of concern for doctors of all specialities. Multidrug resistance leads to the development of a number of complications and an increase in the length of hospital stay [3]. The problem of resistance has been constantly discussed in the medical community for the past 70 years. However, in the last decade, antibiotic resistance has become a truly critical global health issue. The cause of resistance lies in the genetic aspects of pathogens [1, 2]. The full-scale war unleashed by Russia against Ukraine, in addition to its dangerous impact on the lives of Ukrainians, has had a tremendous negative impact on health in general and, in particular, on the effectiveness of recovery of servicemen after injury. Difficult life circumstances make their own adjustments to the medical problem. The war has additionally created problems that existed before. The prolonged development of military events in Ukraine has become the culmination of the development of antibiotic resistance [1, 2].

The military model of the modern healthcare system involves a large number of evacuation stages for traumatised people, which leads to prolonged and additional infection with pathogens. In addition to environmental factors, the patient is constantly surrounded by many people (fellow soldiers, medics, doctors) who may be bacterial carriers of opportunistic pathogens [3].

Heavy metals in bullets, deep and extensive wounds, damaged sanitary and hygienic infrastructure in the combat zone, and forced prolonged stay without qualified medical care contribute to the rapid spread of the infectious process. Mine-blast injuries, gunshot and bullet injuries, shrapnel wounds, compression and strain injuries (CSI), traumatic endotoxemia syndrome (TES), prolonged compression syndrome (PCS), cold injuries (trench foot), combined wounds, and amputations are the main causes of sanitary losses among personnel [3, 5]. Combat mine-blast injuries vary in severity of injury, infectious complications, and, unfortunately, have a high mortality rate [4, 10]. Injuries caused by modern combat weapons are a special type of injury with a rupturing high-kinetic effect and wound channel characteristics, and usually with the formation of "pockets". With such specific injuries, it is not possible to carry out a complete revision and surgical treatment of the wound. The time factor plays a key role in this case [6, 13].

Resistance of microorganisms poses a direct threat when using such modern technologies as joint replacement, application of the Ilizarov compression and distraction apparatus, plates for displaced open comminuted fractures, endoprosthetics with metal implants, as well as

treatment of burns and wound healing with secondary tension. First of all, this applies to pathogens of hospital-acquired infections that are not sensitive to many generations of antibacterial drugs.

Natural migration processes also play a significant role in the spread of resistant pathogens. Unfortunately, pathogens do not recognise state borders. This problem was exacerbated by the coronavirus pandemic, when antibacterial drugs were prescribed en masse to prevent the development of secondary bacterial infection [11, 12]. The complex of these factors has led to an increase in the number of antibiotic-resistant strains of microorganisms, which impairs the overcoming of bacterial pathogens and complicates the prognosis in the current escalation.

Thus, antimicrobial resistance requires immediate intervention not only at the regional or national level, but also at the international level, especially in the current context. Ukraine, like most countries in the civilised world, has committed itself to taking a number of measures to implement the rational use of antimicrobials in medicine in accordance with international standards.

The goal of the global medical community is to curb the spread of resistance, implement regulatory mechanisms and effective monitoring programmes to detect resistant strains.

The international organisation is actively involved in addressing this issue. The Global Drug Resistance Surveillance System (GLASS) calls for systematic data collection in all areas of life. In 2022. WHO updated the list of priority pathogens [8].

The purpose of our study was to investigate the prevalence of antibiotic-resistant forms of the main pathogens of purulent-septic diseases and to assess the spectrum of sensitivity to the list of main and reserve drugs among wounded servicemen treated in medical institutions of the Ministry of Defence and the Ministry of Health of Ukraine.

Materials and methods. Bacteriological studies of servicemen with various types of injuries sustained as a result of hostilities in 2022-2024 were analysed. Clinical strains of microorganisms were isolated from the contents of through wounds, open comminuted fractures, patients with endoprosthetics, metal implants and burns who were treated in the surgical and trauma departments of hospital institutions in the region. The results of 298 samples of biological material were collected and analysed. All patients were male, with an average age of 31.4 – +15.5 years, with soft tissue trauma, endotoxemia syndrome, mine-blast injuries, amputation of upper and lower extremities, open fractures, infectious complications, and osteomyelitis. The average length of bed days was 49-60 days.

The material was collected with a sterile, single-use plastic applicator from the deep layers of the wound and transported in tubes with SARSTEDT AG&Co (Germany) medium. The material was delivered to the bacteriological laboratory within one hour. Microbiological diagnostics consisted of bacterioscopic, bacteriological and biochemical methods of examination.

The bacterioscopic method made it possible to tentatively establish the composition of the microbial landscape of the materials under study, the purity of the isolated culture, tintorial properties and morphological characteristics of microorganisms. The biological material was tested using automated pathogen indication systems Vitek-2 Biomerieux and the classical bacteriological method, followed by sensitivity determination by the disc diffusion method and mandatory monitoring of resistance to drugs that were registered at the hospital, and in severe cases – to the reserve group in the clinical centres of the region.

Results of the study and their discussion. A total of 439 isolates were isolated. In 279 wounded, the infection was treated as community-acquired, as it was associated with prolonged evacuation stages. The highest concentration of bacteria was detected at the boundary between living and necrotic tissues.

There were multidrug-resistant pathogens with extreme resistance, which caused a lot of difficulties in treatment. In such cases, combinations of antibiotics with different mechanisms of action were used (36%).

In 2017, the WHO introduced the Acces, Watch, Reserwe (AWaRe) classification aimed at curbing the trend of increasing antibiotic resistance (AR) in the world and improving the safety and effectiveness of antibacterial use. The classification includes 180 antibiotics, which are divided into three groups: available (Acces), under surveillance (Watch,) and reserve (Reserwe), with their pharmacological classes, anatomical, therapeutic and chemical classification codes, as well as their status in the WHO Essential Medicines List [7, 9].

Resistance monitoring showed that 6 pathogens were responsible for complications: E. coli, Ps. aeruginosa, Acinetobakter baumanii,

Staphylococcus aureus, Klebsiella spp, Streptococcus spp.

The results of monitoring the microflora isolated from the biological material of wounded servicemen in 2022-2023 who received inpatient treatment in specialised hospitals indicate the prevalence of gram-negative microflora (56%) among microorganisms. It is noteworthy that the proportion of Gram(-) bacteria decreased in autumn and winter. In the spring and summer, the proportion of Gram-negative pathogens isolated increased to 68%, mainly due to E. coli (28%), Klebsiella spp. (16.4%), Asinetobacter spp. (12.3%), Pseudomonas spp. (11.3%). Anaerobic infection accounted for 6.4%. Other pathogens accounted for 25.6%. It should be noted that the resistance of pathogens was not equivalent in servicemen who were in different regions of the military conflict.

E. coli was highly resistant to aminopenicillins (46.2%) and especially to tetracyclines (97.0%). Escherichia coli were susceptible to teigecycline in 38.7% and amikacin in 29.7%. Penicillins were not susceptible in 100% of cases, as well as carbenicillin, ticaricillin with clavulanic acid), and intermediate susceptibility was determined to cephalosporins. Meropenem remained inactive to the isolates in most cases.

The isolated Klebsiella spp. strains showed a high frequency of resistance even to cephalosporins. They were 100% resistant to penicillins, fluoroquinolones, and piperacillin-tazobactam. The carbopenems (meropenem, imopenem) have high activity against Klebsiella pneumoniae – resistance is less than 14% in all cases. Cephalosporins were resistant in 41.1% of Klebsiella pneumoniae, aminoglycosides (amikacin, gentamicin) in 75.9% of Klebsiella pneumoniae were resistant, and 79.0% were resistant to fluoroquinolones (ciprofloxacin, levofloxacin).

The list of antibacterial drugs active against Pseudomonas aeruginosa is much shorter. New combinations of ceftazidime/avibactam (Zavicefta), ceftolozan/tazobactam (Zerbaxa) are actively used as the best option for the treatment of multidrug-resistant Gram-negative infections caused by carbenicillin-resistant Enterobacteriaceae and drug-resistant Ps. aeruginosa. In 9.0%, ceftazidime, meropenem, carbenicillin, and cefepime had intermediate activity against the isolated Ps. aeruginosa isolates.

Cefiderocol showed antibacterial effect against gram-negative bacteria, including Asinetobacter spp. Also, it was active against Hemophilis spp. which are the causative agents of upper respiratory tract inflammation in polygamous infection, especially in patients on ventilators.

Plazomicin (Zemdri), a new broad-spectrum aminoglycoside, was effective in 80.4% of patients, especially in patients with concomitant bacterial infection of the kidneys and urinary tract.

Pr.mirabilis was susceptible to amikacin, phosphomycin, fluoroquinolones, meropenem. It was insensitive to penicillins, cephalosporins, and piperacillin-tazobactam.

Gram-positive pathogens isolated in infectious toxic shock (S. aureus, E. faecalis, Streptococcus spp.) were sensitive to vancomycin, linezolid, phosphomycin, teicoplanin. In case of complicated course of the infection, combinations of different groups of antibacterial drugs and a reserve group were used.

A high frequency of methicillin-resistant staphylococcus aureus strains (57.8%), resistant to all betalactam antibiotics (61.9%) and macrolides (67.0%) was observed. The highest number of methicillin-resistant S. aureus strains (MRSA) was detected in wounded who were undergoing long-term treatment.

In association with bacterial infection, fungal infection was identified in many cases (22.0%). Thus, Candida albicans was resistant to fluconazole in 28%, amphotericin B in 31%, and caspofungin in 23%. Candida auris was identified in 5.2% of cases and was also resistant to many antifungal drugs (43.0%).

The proportion of non-fermenting Gram(-) bacteria in the etiological structure of bacterial infections of military personnel in medical institutions of various profiles was determined. The levels and spectra of antibiotic resistance in relation to commonly used antibacterial drugs were determined.

Cefiderocol (a reserve drug) was prescribed to critically ill patients, as it was effective in treating patients with carbepenem resistance. Cefiderocol had antibacterial activity against gram-negative bacteria, including Acinetobacter spp. and Pseudomonas spp. It was also active against Haemophilis spp. in patients on mechanical ventilation devices (MVDs). The new broad-spectrum aminoglycoside was effective in 80% of patients, especially in patients with secondary kidney and urinary tract infections. Representatives of Enterococcus faecium, Klebsiella pneumoniae, Acinetobacter baumanii, Staphylococcus aureus, Pseudomonas aeruginosa, Enterobacter spp. were resistant to most drugs.

Pseudomonas and Acinetobacter were sensitive to colistin.

S. saprophyticus is the only gram-positive pathogen that is sensitive to tegecycline and vancomycin and resistant to penicillins, cephalosporins, and macrolides.

An increase in the level of resistance of almost all strains to oxacillin (54.0-89.0%), azithromycin (42.0-71.0%), and aminoglycosides (76.0%) was detected. Braxone was active in 93.0% of cases.

Prospects for further research

It is planned to continue studying the effectiveness of etiotropic therapy of purulent inflammatory diseases in the context of further escalation of the military conflict with Russia in order to improve the treatment of patients and wounded, as well as to prevent the formation of hospital strains of pathogens.

Conclusions.

1. The issue of etiotropic therapy of purulent inflammatory diseases in the context of war remains a growing problem for both patients and doctors.

2. Comparative results of bacteriological studies of patients in 2022 and 2024 suggest a high level of circulation of multidrug-resistant clinical isolates.

3. In monitoring patients in 2023, reserve group drugs were prescribed 1.8 times more often than in 2022, and 4.1 times more often in 2024.

4. Microbiological monitoring data allows timely detection of the formation of hospital-acquired pathogen strains and enables epidemiological analysis and effective management. Spread monitoring is one of the key measures in the fight against drug-resistant pathogens.

5. It should be noted the importance of the work of hospital epidemiologists in infection control to prevent the emergence of multidrug-resistant strains of microorganisms and the development of hospital-acquired infections.

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