DOI: https://doi.org/10.17816/brmma207771

Research article

CHARACTERISTICS OF ANTIBIOTIC RESISTANCE OF INFECTIOUS PATHOGENS IN THE WOUNDED

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ABSTRACT

This study examines the etiological structure and antibiotic resistance features of pathogens causing infectious complications in wounded patients receiving specialized medical care are considered. A total of 3845 clinical isolates were analyzed from wounded individuals admitted t o a multidisciplinary hospital for treatment. The analysis revealed that polyresistant pathogens, namely, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, and *Acinetobacter baumannii* were predominant among the isolated microorganisms. The prevalence of *Acinetobacter baumannii* varied based on the type of clinical material, with higher rates observed in wounds and respiratory, and urinary tract discharges. The polyresistant clinical isolates of *Acinetobacter baumannii* were sensitive to tigecycline and polymyxin, while *Klebsiella pneumoniae* and *Pseudomonas aeruginosa* were sensitive to polymyxin only. A comparison of the 2022 data with a previous study conducted in 2020 on wound discharges revealed a significant shift in the spectrum of pathogens causing wound infections. This shift involved an increase in the proportion of *Acinetobacter spp.*, *Bacillus spp.*, *Enterococcus spp.*, *Pseudomonas aeruginosa*, and *Klebsiella pneumoniae*, as well as a decrease in the proportion of certain gram-negative bacteria, including *Proteus spp.* and *Escherichia coli.* Additionally, a notable five-fold reduction in the proportion of *Streptococcus spp.* and *Staphylococcus aureus* was observed. It is likely that early empirical therapy for combat wounds effectively prevents the development of wound infections associated with these pathogens. Bloodstream infections were primarily caused by coagulase-negative staphylococci (34.5%) and *Klebsiella pneumoniae* (27.8%). Notably, 80% of Staphylococcus spp. isolates were methicillin-resistant. The prolonged course of infectious complications associated with polyresistant strains and the challenges in selecting appropriate antibacterial therapy may contribute to the circulation of antibiotic-resistant nosocomial strains within the hospital environment. Therefore, it is crucial to increase the vigilance of the epidemiological service in addressing the high frequency of polyresistant pathogens to implement timely antiepidemic measures. Overall, these findings indicate the involvement of polyresistant gram-negative bacteria in the development of infectious complications during the inpatient treatment of wounded individuals.

Keywords: pathogens of infectious complications; microbiological monitoring; polyresistant gram-negative bacteria; antibiotic-resistant nosocomial strains; antiepidemic measures; injury; specialized medical care; stages of medical evacuation.

To cite this article:

Kryukov EV, Golovko KP, Markevich VYu, Suborova TN, Nosov AM, Khugaev LA, Melnikova EV, Sidelnikova OP. Characteristics of antibiotic resistance of infectious pathogens in the wounded. *Bulletin of the Russian Military Medical Academy.* 2023;25(2):193–202. DOI: https://doi.org/10.17816/brmma207771

Received: 09.02.2023 **Accepted:** 06.05.2023 **Published:** 15.06.2023

УДК 614.2:579.61:615.036

DOI: https://doi.org/10.17816/brmma207771

Научная статья

ХАРАКТЕРИСТИКА АНТИБИОТИКОРЕЗИСТЕНТНОСТИ ВОЗБУДИТЕЛЕЙ ИНФЕКЦИОННЫХ ОСЛОЖНЕНИЙ У РАНЕНЫХ

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Резюме

Рассмотрены особенности этиологической структуры и антибиотикорезистентности возбудителей инфекционных осложнений у раненых на этапе оказания специализированной медицинской помощи. Исследованы 3845 клинических изолятов, полученных от поступивших на лечение в многопрофильный стационар раненых. Установлено, что в спектре выделенных микроорганизмов преобладали полирезистентные возбудители *Klebsiella pneumoniae, Pseudomonas aeruginosa* и *Acinetobacter baumannii*, удельный вес которых варьировал в зависимости от вида клинического материала. Данные бактерии преобладали в спектре микроорганизмов, выделенных из ран, а также отделяемого дыхательных и мочевыводящих путей. Полирезистентные клинические изоляты *Acinetobacter baumannii* были чувствительны только к тигециклину и полимиксину, *Klebsiella pneumoniae* и *Pseudomonas aeruginosa* — только к полимиксину. При сопоставлении данных 2022 г. с результатами исследования раневого отделяемого, проведенного в 2020 г., выявлено резкое изменение спектра возбудителей раневой инфекции: увеличение доли *Acinetobacter spp., Bacillus spp., Enterococcus spp., Pseudomonas aeruginosa, Klebsiella pneumoniae* и снижение доли ряда грамотрицательных бактерий, в том числе *Proteus spp.* и *Esherichia coli,* а также выраженное 5-кратное сокращение доли *Streptococcus spp.* и *Staphylococcus aureus*. Вероятно, эмпирическая терапия боевых ранений на ранних этапах оказания медицинской помощи эффективно препятствует развитию раневых инфекций, связанных с данными возбудителями. Среди возбудителей инфекции кровотока лидировали коагулазоотрицательные стафилококки (34,5 %) и *Klebsiella pneumoniae* с показателем 27,8 %. При этом доля метициллинрезистентных *Staphylococcus spp.* составила 80 %. Длительное течение инфекционных осложнений, связанных с полирезистентными штаммами возбудителей, сложность подбора рациональной антибактериальной терапии могут поддерживать циркуляцию антибиотикорезистентных внутрибольничных штаммов в госпитальной среде. Необходимо усиление внимания эпидемиологической службы к проблеме высокой частоты выделения полирезистентных возбудителей для своевременного проведения противоэпидемических мероприятий. Таким образом, полученные данные свидетельствуют об участии полирезистентных грамотрицательных бактерий в развитии инфекционных осложнений у раненых на этапе стационарного лечения.

Ключевые слова: возбудители инфекционных осложнений; микробиологический мониторинг; полирезистентные грамотрицательные бактерии; антибиотикорезистентные внутрибольничные штаммы; противоэпидемические мероприятия; ранение; специализированная медицинская помощь; этапы медицинской эвакуации.

Как цитировать:

Крюков Е.В., Головко К.П., Маркевич В.Ю., Суборова Т.Н., Носов А.М., Хугаев Л.А., Мельникова Е.В., Сидельникова О.П. Характеристика антибиотикорезистентности возбудителей инфекционных осложнений у раненых // Вестник Российской военно-медицинской академии. 2023. Т. 25, № 2. С. 193–202. DOI: https://doi.org/10.17816/brmma207771

Рукопись получена: 09.02.2023 **Рукопись одобрена:** 06.05.2023 **Опубликована:** 15.06.2023

ЭКО•ВЕКТОР

BACKGROUND

Since the end of World War II, there has been a significant evolution in firearms and explosive ammunition. Consequently, the number of victims with extensive injuries and the frequency of multiple and combined injuries has increased [1]. The most common and dangerous complication of combat injuries is surgical infection. Despite the improvements in personal and collective protective equipment [2], the use of broad-spectrum antibiotics, and modern medical and surgical care, wound infections have a significant impact on the treatment and outcomes of wounds [3–6].

Combat wounds are the most complex type of wounds, caused by uncontrolled tissue damage of various and multiple localizations, exposing sterile areas of the body to contamination by many bacteria. The development of infectious complications of combat wounds is caused by contamination during injury with bacteria from the body's intrinsic microbiota or those entering the wound from the environment along with exogenous agents (bullets, tissue fragments, dust, dirt, and water), or from later nosocomial sources [4, 7, 8]. The range of etiological agents in contaminated gunshot wounds is influenced by the wound etiology, the injured area of the body, the time interval between the wound and primary surgical treatment, climatic factors, time of the year, geographical area, and sanitary conditions [9].

Provision of medical care to the wounded in medical hospitals entails the risk of additional infection with multidrug-resistant pathogens of nosocomial infections, the role of which is now particularly significant throughout the world. Antibiotic resistance is of enormous socioeconomic importance and is considered a threat to national security in developed countries [10].

The diversity of microorganisms in modern combat wounds is unique to each military conflict. Climatic and geographical aspects of the scene of military operations, the use of modern types of weapons, and treatment methods influence the microflora of wounds [6, 9, 11, 12]. If infection occurs, the wound does not heal, and wound care costs increase. The fact that the microflora of wounds shifts in favor of bacteria responsible for nosocomial infections indicates an intrahospital association between these changes [13–15].

Identification of microorganisms that cause wound infection and associated infectious complications is crucial. This information may help improve strategies to combat infections that complicate the treatment of combat injuries.

This study aimed to identify the characteristics of the etiological structure and antibiotic resistance of pathogens causing infectious complications in wounded patients during the provision of specialized medical care.

MATERIALS AND METHODS

Samples of wound discharge, blood, urine, and samples taken during examination of the respiratory tract and lungs (sputum, bronchial lavage, broncho-alveolar lavage, and pleural cavity discharge) were collected from the wounded patients who received inpatient treatment in the clinics of a multidisciplinary military medical hospital from 03/01/2022 to 07/30/2022. The study was conducted at the bacteriological department of the Center for Clinical Laboratory Diagnostics of the S.M. Kirov Military Medical Academy. Sampling of clinical material and primary inoculation were performed in accordance with the requirements of regulatory documents. Microorganisms were isolated from samples of clinical material of the wounded, including 62.4% of cases from wound discharge, 22.6% of cases of bacteria and micromycetes isolated from respiratory tract discharge and (or) urine, and 15% from patients whose wound infections were accompanied by positive blood inoculation. To identify bacteria, a BactoSCREEN mass spectrometer from Litech (Russia) was used. A total of 3845 strains of microorganisms were isolated from samples of clinical material, comprising 2217 (57.7%) from wound discharge, 993 (25.8%) from respiratory tract discharge, 317 (8.2%) from blood, and 318 (8.3%) from urine.

The sensitivity of clinical isolates to antibiotics was determined using an automatic microbiological analyzer Vitek-2 from bioMerieux (France) or by the disk diffusion method. The results were assessed based on the interpretation criteria presented in the 2021 recommendations in Russia [16]. The results were presented as relative frequency and distribution values. The significance of differences in frequency indicators was assessed using Student's *t*-test.

RESULTS AND DISCUSSION

Causative agents of infectious complications isolated from wounded patients from clinical samples. Among the microbial isolates, 2487 (64.7%) were Gram-negative bacteria (GNB), 1195 (31.1%) were Gram-positive bacteria (GPB), and 163 (4.2%) were micromycetes. GPB predominated only among microorganisms isolated from blood; in other types of clinical material, GNB dominated, constituting 64.7% of isolates in wound discharge samples, 69.2% of isolates in sputum, and 73.6% of isolates in urine samples. The currently most common GNB pathogens of nosocomial infections, namely, *Klebsiella pneumoniae, Acinetobacter baumannii*, and *Pseudomonas aeruginosa*, accounted for more than 50% of all isolated microorganisms.

On average, three strains of wound infection pathogens were isolated simultaneously or sequentially from the same patient with microbial growth in the wound discharge. This

DOI: https://doi.org/10.17816/brmma207771

can be attributed to the occurrence of bacterial associations in the development of infectious complications, and longer treatment time for seriously injured patients, during which a change in microflora could occur [12–14, 17, 18].

Among the causative agents of wound infection, GNB accounted for 64.7% (1436), GPB accounted for 33.8% (750), and micromycetes accounted for 1.4% (32). *Klebsiella pneumoniae* isolates had the highest proportion of 21.6% (479), followed by *Acinetobacter spp*. with 20.8% (4618), and representatives of the genera *Pseudomonas* had a proportion of 13.8% (306), *Enterococcus* had a proportion of 12.4% (275), and *Staphylococcus* accounted for 9.6% (214). In newly admitted wounded patients, Gram-positive spore-forming rods of the genera *Bacillus* or *Paenibacillus* were isolated, and accounted for 7.3% (162) of the isolates (Table 1).

From the year 2020 to 2022, there was a significant change in the spectrum of clinical isolates that cause wound infections. A significant increase in the proportion of *Acinetobacter spp., Bacillus spp., Enterococcus spp., P. aeruginosa,* and *K. pneumonia,* and a decrease in the proportion of GNBs, including *Proteus spp*. and *Escherichia coli*, as well as a 4–5-fold decrease in the proportion of *Streptococcus spp*. and *Staphylococcus aureus* were observed. Empirical treatment of combat wounds in the early stages of medical care can effectively prevent the development of wound infections associated with these pathogens (Table 2).

In 22.6% of the wounded patients, microorganisms were isolated from samples of respiratory tract secretions and/or urine. As a rule, these were patients in intensive care units who, due to the severity of their condition, were under artificial lung ventilation and had a urinary catheter installed. Considering repeated studies on samples of respiratory tract secretions (sputum, bronchial washings, broncho-alveolar lavage, and pleural cavity secretions), 993 strains of bacteria and micromycetes were isolated, among which the prevalence of GNB was 69.2% (687), that of GPB was 21.9% (217), and that of micromycetes were 9% (89). The isolates of *K. pneumoniae* (28.6%), *Pseudomonas spp*. (17.9%), and *Acinetobacter spp*. (15.5%) represented the highest proportion. During the same period, 318 strains of bacteria and micromycetes were isolated from urine samples. Among them, the prevalence of GNB exceeded that of the respiratory tract and amounted to 73.6% (234), whereas that of GPB was 16.7% (53), and the prevalence of

Table 1. Spectrum of infectious complication causative agents isolated from clinical specimens taken from casualtiess
Таблица 1. Спектр возбудителей инфекционных осложнений, выделенных из образцов клинического материала у раненых

Genus and species of pathogen	Number of isolates, *n* = 3845		Wound discharge, *n* = 2217		Sputum, *n* = 993		Urine, *n* = 318		Blood, *n* = 317	
	n	%	*n*	%	*n*	%	*n*	%	*n*	%
Klebsiella pneumoniae	949	24.7	479	21.6	284	28.6	98	30.8	88	27.8
Acinetobacter baumannii	652	17.0	462	20.8	154	15.5	25	7.9	12	3.8
Pseudomonas aeruginosa	562	14.6	306	13.8	178	17.9	66	20.8	12	3.8
Enterococcus faecalis	197	5.1	157	7.1	12	1.2	17	5.3	11	3.5
Bacillus spp., Paenibacillus spp.	170	4.4	162	7.3	7	0.7	0	0	1	0.3
Enterococcus spp.	167	4.3	118	5.3	13	1.3	20	6.3	16	5.0
Candida spp.	163	4.2	31	1.4	89	9.0	31	9.7	11	3.5
Staphylococcus aureus	137	3.6	93	4.2	34	3.4	1	0.3	8	2.5
Staphylococcus epidermidis	122	3.2	51	2.3	9	0.9	6	1.9	55	17.4
Esherichia coli	110	2.9	84	3.8	11	1.1	9	2.8	6	1.9
Streptococcus spp.	106	2.8	13	0.6	86	8.7	2	0.6	4	1.3
Staphylococcus haemolyticus	85	2.2	29	1.3	8	0.8	5	1.6	43	13.6
Corynebacterium spp.	83	2.2	51	2.3	26	2.6	0	0	6	1.9
Staphylococcus spp.	71	1.8	40	1.8	4	0.4	2	0.6	26	8.2
Other GNBs	70	1.8	31	1.4	32	3.2	4	1.3	4	1.3
Enterobacter spp.	65	1.7	51	2.3	8	0.8	6	1.9	1	0.3
Proteus spp.	59	1.5	24	1.1	9	0.9	25	7.9	1	0.3
Other GPBs	57	1.5	33	1.5	18	1.8	0	0	6	1.9
Burkholderia spp.	20	0.5	2	0.1	11	1.1	1	0.3	6	1.9

DOI: https://doi.org/10.17816/brmma207771

micromycetes was 9.7% (31). The highest specific gravity, as in respiratory tract infections, was recorded for the isolates of *K. pneumoniae* (30.8%), *Pseudomonas spp*. (20.8%), and *Acinetobacter spp*. (7.9%) (Table 1). These features of the spectrum can be explained by the addition of pathogens of nosocomial infections [6, 18].

In 15% of the patients, wound infection was accompanied by bacteremia. Considering repeated studies, 317 strains of bacteria were isolated from blood samples, among which GNB constituted 41% (130), GPB 55.5% (176), and micromycetes consituted 3.5% (11). The isolates of *K. pneumoniae* (27.8%), *S. epidermidis* (17.4%), and *S. haemolyticus* (13.6%) had the highest proportion. There were no significant differences in the frequency of isolation of the most common pathogens of bloodstream infections between 2022 and 2020, with the exception of the more frequent isolation of coagulase-negative staphylococci and the rarer isolation of *A. baumannii* and *E. faecalis* (Table 3).

Antibiotic susceptibility of clinical isolates of GNB. Regardless of the source of isolation, the sensitivity of clinical isolates of *Acinetobacter spp*. to ciprofloxacin did not exceed 10%, and that to ampicillin/sulbactam, 3–4th generation cephalosporins, aminoglycosides, carbapenems, and trimethoprim/sulphamethoxazole did not exceed 20–30%. Only tigecycline and polymyxin retained 70–90% antimicrobial activity (Fig. 1).

Klebsiella pneumoniae strains were resistant to 3–4th generation cephalosporins, ciprofloxacin, and phosphomycin. Aminoglycosides, carbapenems, and trimethoprim/sulphamethoxazole retained 25–30% activity against it.

Table 2. Variation in the spectrum of infectious complication causative agents found in 2022, compared to data of 2020 (in %)
Таблица 2. Изменение спектра возбудителей раневой инфекции в 2022 г. по сравнению с данными 2020 г., %

Genus and species of pathogen	2020 г., *n* = 2490	2022 г., *n* = 2217	*p* =
Acinetobacter spp.	6	20.8	0.001
Bacillus spp.	0.4	7.3	0.001
Enterococcus spp.	2.2	5.3	0.001
Pseudomonas aeruginosa	9.5	13.8	0.001
Klebsiella pneumoniae	16.5	21.6	0.001
Enterococcus faecalis	4.8	7.1	0.001
Enterobacter spp.	1.2	2.3	0.004
Corynebacterium spp.	2.3	2.3	1.0
Other GPBs	1.8	1.5	0.421
Candida spp.	1.9	1.4	0.181
Proteus spp.	2.4	1.1	0.001
Esherichia coli	7.3	3.8	0.001
Staphylococcus spp.	11.9	5.4	0.001
Streptococcus spp.	5.2	0.6	0.001
Other GNBs	7.4	1.5	0.001
Staphylococcus aureus	19.2	4.2	0.001

Table 3. Variation in the spectrum of bloodstream infection agents in 2020–2022 (in %)
Таблица 3. Изменение спектра возбудителей инфекции кровотока в 2020–2022 гг., %

Genus and species of pathogen	2020, *n* = 558	2022, *n* = 317	*p* =
Staphylococcus spp.	25.6	39.1	0.001
Klebsiella pneumoniae	26	27.8	0.562
Acinetobacter baumannii	7.9	3.8	0.017
Pseudomonas aeruginosa	2.9	3.8	0.469
Staphylococcus aureus	4.5	2.5	0.136
Enterococcus faecalis	7.5	3.5	0.017
Candida spp.	4.7	3.5	0.398
Other	20.9	16	0.076

Susceptibility to tigecycline exceeded 40% only for strains isolated from wounds and blood. The isolates retained 90% sensitivity only to polymyxin (Fig. 2).

The resistance of *P. aeruginosa*, regardless of the type of clinical material, was extreme. The sensitivity of *P. aeruginosa* isolates to all antibiotics tested did not exceed 20%. Only polymyxin was effective against it (Fig. 3).

Staphylococcus aureus isolated from blood was sensitive to almost all antibiotics studied, with the exception of penicillin. This reflects the community-acquired nature of the infection. Coagulase-negative *Staphylococcus spp.*, which were predominated by *S. epidermidis* and *S. haemolyticus*, were significantly more resistant. The proportion of methicillin-resistant isolates was 80%, only approximately 20% of

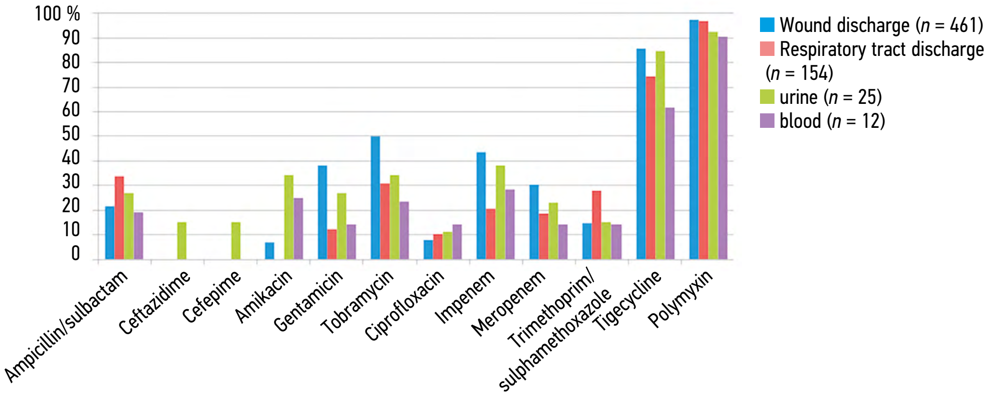

Fig. 1. Antibiotic sensitivity of clinical isolates *Acinetobacter spp.* isolated from clinical specimens
Рис. 1. Чувствительность к антибиотикам клинических изолятов *Acinetobacter spp*., выделенных из образцов клинического материала

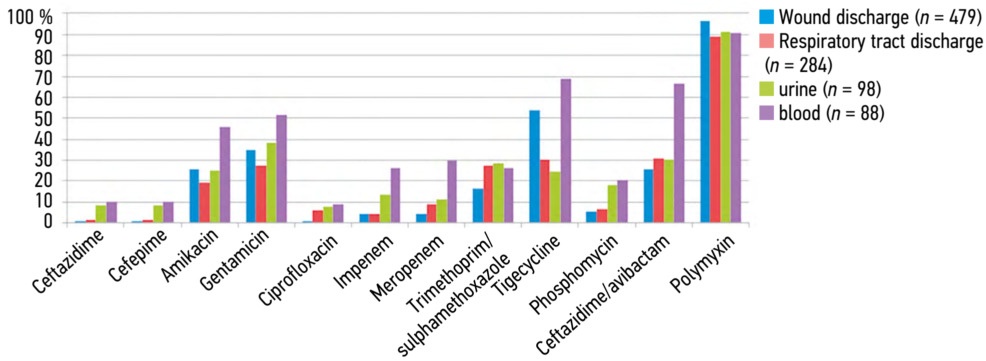

Fig. 2. Antibiotic sensitivity of clinical isolates *K. pneumoniae* isolated from clinical specimens
Рис. 2. Чувствительность к антибиотикам клинических изолятов *K. pneumoniae*, выделенных из образцов клинического материала

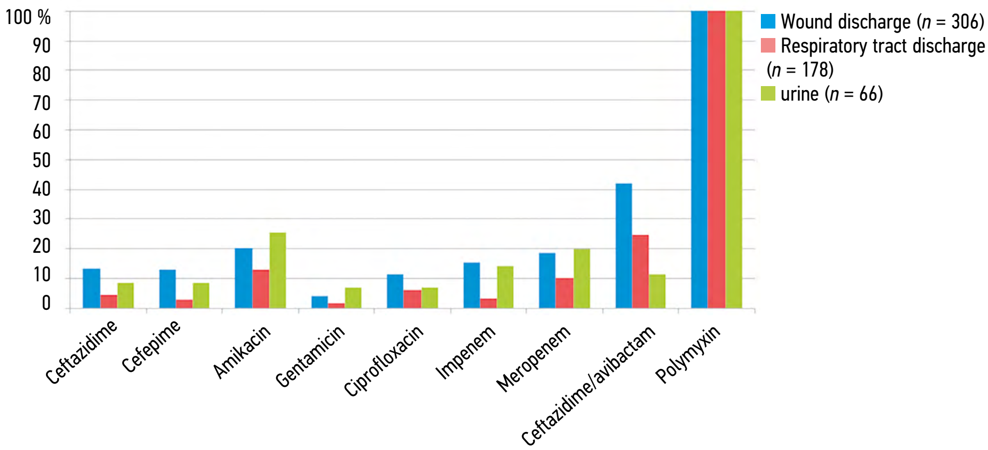

Fig. 3. Antibiotic sensitivity of clinical isolates *P. aeruginosa* isolated from clinical specimens
Рис. 3. Чувствительность к антибиотикам клинических изолятов *P. aeruginosa*, выделенных из образцов клинического материала

DOI: https://doi.org/10.17816/brmma207771

isolates were sensitive to fluoroquinolones, and 35% were sensitive to gentamicin and clindamycin. All staphylococci isolates were sensitive to tigecycline, vancomycin, and linezolid. Clinical isolates of enterococci from blood were also resistant to fluoroquinolones, and only 17% of them retained sensitivity to agents of this group. Sensitivity to vancomycin and linezolid was 90%, and that to tigecycline was 100%.

The study of the spectrum and sensitivity to antimicrobial drugs of microflora isolated from wounds, respiratory and urinary tract secretions, and the blood of wounded patients at the stage of hospital treatment revealed the leading role of multidrug-resistant Gram-negative bacteria. The leading role of *K. pneumoniae* in the development of septic complications was also shown.

Although humanity began to develop treatment methods almost simultaneously with the advent of weapons, the need to develop new medicines and principles for the treatment of infected wounds accompanies all military conflicts. Ineffectiveness of treatment is caused by the biological properties of the causative agents of infectious complications and their change or adaptation to new chemotherapy drugs or methods of treatment. Resistance of pathogens to antibiotics leads to long-term complications and multiple repeated inoculations of the same pathogen, which indicates the difficulty of selecting a rational antibacterial therapy [8, 10, 19].

The microflora composition of combat wounds is constantly changing. The leading causative agents of wound infections were bacteria of the genus *Clostridium* during the First World War, and streptococci and *S. aureus* during the Second World War. The development of new treatment methods, including the use of antiseptics and antibiotics, led to a decrease in the etiological role of these pathogens, but they were replaced by Gram-negative bacteria predominated by *A. baumannii* during the wars in Korea, Vietnam, Iraq, Kuwait, and Afghanistan [18–22]. The main feature of these isolates was multiple antibiotic resistance. Research has substantiated nosocomial transmission of microorganisms and the involvement of medical personnel in this process since the Second World War. The microbial load of Gram-negative rods increases with time elapsed from the moment of injury, i.e., the range of microorganisms changes during the treatment process [8, 11, 14, 15].

One of the factors in the spread of resistant bacteria among the wounded is the duration and multi-stage nature of evacuation. Systems for treating the wounded in the field, a drainage system, a system for distributing the wounded and sick, and a system of staged treatment with evacuation as referred can exist in parallel and be used depending on the specific conditions of the combat situation [23], but measures aimed at preventing infectious complications should be initiated from the moment of injury or admission of the wounded to the hospital [4, 17, 24]. The nosocomial microflora of a hospital largely determines the severity of the wound process, therefore, identifying microorganisms that cause wound infection and accompanying infectious complications is critical. Data on the microbial landscape of wounds throughout their treatment are necessary to determine the approach of antibacterial therapy and infection control measures in medical institutions. This information may be used to improve strategies to combat infections that complicate the treatment of combat injuries.

CONCLUSIONS

1. Among 3845 microorganisms isolated from admitted wounded patients, three Gram-negative pathogens of nosocomial infections were most prevalent, namely, *K. pneumoniae, A. baumannii,* and *P. aeruginosa*, which accounted for more than 50% of all isolates. These bacteria predominated in the range of microorganisms isolated from wounds, and discharge from the respiratory and urinary tracts. Multidrug-resistant clinical isolates of *A. baumannii* were sensitive only to tigecycline and polymyxin, whereas *K. pneumoniae* and *P. aeruginosa* were sensitive only to polymyxin.

2. A reduction in the proportion of *Proteus spp*. and *E. coli*, as well as *Streptococcus spp*. and *Staphylococcus aureus* in the spectrum of wound infection pathogens in comparison with peacetime data was observed. Antibacterial prevention of infectious complications in the early stages of medical care probably effectively prevents the development of wound infections associated with these pathogens. An increase in the proportion of *Acinetobacter spp., Bacillus spp., Enterococcus spp., P. aeruginosa, K. pneumoniae* was noted.

3. Among the causative agents of bloodstream infections, *coagulase*-negative staphylococci (34.5%) and *K. pneumoniae* were the most common, with an indicator of 27.8%. The proportion of methicillin-resistant *Staphylococcus spp*. amounted to 80%.

4. The long course of infectious complications associated with multidrug-resistant strains of pathogens and the difficulty in selecting rational antibacterial therapy can support the circulation of antibiotic-resistant nosocomial strains in the hospital environment. It is necessary to increase the awareness of epidemiological service to the problem of the high frequency of isolation of multidrug-resistant pathogens for the timely implementation of anti-epidemic measures.

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