

Antimicrobial resistance and genomic epidemiology of bacterial war-wound infections: Ukraine, 2014–2023

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The aim of the study was to identify the dominant clonal lineages of pathogens causing combat wounds and to determine their antimicrobial resistance determinants for the purpose of optimizing antimicrobial drug administration in wartime.

Materials and methods. Microbiological monitoring of combat wound contents was carried out in patients of three medical hospitals in the central region of Ukraine during 2014–2023. Molecular genetic studies involving whole genome sequencing (WGS) of isolated cultures using Next-Generation Sequencing (NGS), followed by multilocus genotyping of genome sequences and gene identification, were performed at the Walter Reed Army Institute of Research (USA). Antibiotic sensitivity was determined using the disc diffusion method in accordance with the EUCAST recommendations.

Results. The results of bacteriological studies of combat wounds of the limbs and soft tissues of the torso during 2022 and 2023 have shown that *A. baumannii* (35.7 %), *K. pneumoniae* (20.7 %), and *P. aeruginosa* (14.9 %) were the most common organisms cultured. For *A. baumannii*, 95.6 % of isolates were multidrug-resistant (MDR), and 41.1 % were classified as extensively drug-resistant (XDR). Genome sequencing identified several high-risk international clones, including ST2, ST78 and ST1077, which carried the carbapenemase genes *bla*_{OXA-23}, *bla*_{OXA-72} and the 16S methyltransferase gene *armA*. Among the various strains of *P. aeruginosa*, isolates of globally distributed clonal lines ST235, ST357, ST773, and ST1047 have been identified.

The *K. pneumoniae* isolates belonged to five distinct clonal groups: ST395, ST307, ST147, ST39, and ST23. Most of these isolates carried carbapenemases and were classified as MDR and XDR.

Conclusions. This study analyzed bacterial pathogens from combat wounds in Ukraine (2014–2023), revealing a dominance of MDR/XDR Gram-negative organisms, primarily *Acinetobacter baumannii*, *Pseudomonas aeruginosa* and *Klebsiella pneumoniae*. Whole-genome sequencing identified the emergence of high-risk international clones (e. g. *A. baumannii* ST2, ST78, ST1077; *P. aeruginosa* ST235, ST357, ST773, ST1047; *K. pneumoniae* ST147, ST307, ST395), many carrying *bla*_{OXA}, *bla*_{NDM}, 16S rRNA methyltransferases and, in *K. pneumoniae*, hypervirulence markers. The findings underscore the close association between armed conflict and the amplification of antimicrobial resistance, driven by high antibiotic consumption, complex evacuation pathways, and nosocomial transmission in overstretched healthcare systems.

Keywords:

antibiotics, resistance, genome sequencing, high-risk clones, infection, combat trauma.

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Антимікробна резистентність і геномна епідеміологія бактеріальних інфекцій у військовому контексті: Україна, 2014–2023

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Мета роботи – виявлення клональних ліній збудників інфекцій, що домінують, бойових ран під час війни в Україні, визначення детермінант стійкості виділених мікроорганізмів до антибіотиків для ефективного адміністрування антимікробних препаратів у воєнний час.

Матеріали і методи. Молекулярно-генетичні дослідження з секвенування генома (WGS) виділених культур методом «нового покоління» з наступним багатолуксним типуванням послідовностей генома й ідентифікацією генів здійснено у лабораторії Військового інституту досліджень ім. Волтера Ріда (США). Чутливість до антибіотиків визначено диско-дифузійним методом відповідно до рекомендацій EUCAST.

Результати. За результатами дослідження вмісту бойових ран кінцівок і м'яких тканин тулуба, що здійснене у 2022–2023, підтвердили тенденцію до домінування *A. baumannii* (35,7 %) та *K. pneumoniae* (20,7 %), *P. aeruginosa* виділено у 14,9 % випадків. Вивчили профілі фенотипової резистентності, встановили, що *A. baumannii* у 95,6 % випадків належали до мультирезистентних (MDR), а 41,1 % штамів характеризувалися надзвичайною резистентністю (XDR). Секвенування генома ізолятів *A. baumannii* визначило 8 різних клональних ліній: ST2, ST78 і ST1077, – що є носіями карбапенемаз *bla*_{OXA-23}, *bla*_{OXA-72} та гена *armA*. Серед штамів *P. aeruginosa* виділено ізоляти клональних ліній ST235 і ST357, ST773, ST1047, що мають глобальне поширення і є носіями генетичних детермінант продукції беталактамаз розширеного спектра дії класу A, D та металобеталактамаз. Виділені ізоляти *K. pneumoniae* належали переважно до п'яти клональних груп ST395, ST307, ST147, ST39, ST23, що переважно були носіями карбапенемаз і за фенотиповою чутливістю належали до MDR і XDR штамів.

Ключові слова:

антибіотики, резистентність, секвенування генома, клони високого ризику, інфекція, бойова травма.

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Висновки. Проаналізовано бактеріальні патогени, виділені з бойових ран українських військовослужбовців (2014–2023 рр.). Встановлено домінування мультирезистентних (MDR) та екстремально резистентних (XDR) грамнегативних мікроорганізмів, переважно *Acinetobacter baumannii*, *Pseudomonas aeruginosa* та *Klebsiella pneumoniae*. Повногеномне секвенування дало змогу виявити міжнародні високоризикові клони (*A. baumannii* ST2, ST78, ST1077; *P. aeruginosa* ST235, ST357, ST773, ST1047; *K. pneumoniae* ST147, ST307, ST395), і багато із них несуть гени *bla*_{OXA1}, *bla*_{NDM1}, метилтрансфераз 16S рРНК, а *K. pneumoniae* – ще й маркери гіпервірулентності. Результати дослідження підтверджують зв'язок між збройним конфліктом і поширенням антимікробної резистентності, що зумовлене високим рівнем приймання антибіотиків, складними маршрутами медичної евакуації та внутрішньолікарняною передачею у переважаних системах охорони здоров'я.

A significant challenge in contemporary military medicine pertains to the management of infectious complications arising from combat injuries, which affect more than a third of wounded individuals. The complexity of resolving this issue is associated with the global dissemination of antibiotic resistance in bacterial pathogens. The World Health Organization (WHO) has included antibiotic resistance in its list of the 10 major threats to global health. In 2015, the WHO initiated a global surveillance system for antimicrobial resistance (GLASS), encompassing over 120 countries. According to the findings of GLASS, even in the relatively peaceful year of 2019, antibiotic resistance was the direct cause of 1.27 million deaths worldwide and contributed to further 4.95 million deaths [1].

It is evident that a discernible correlation has been observed between the propagation of antibiotic resistance and geopolitical military conflicts over the past fifty years [2]. The first reported cases of penicillin-resistant wound pathogens in humans with military injuries were first reported during World War II. While the rate of staphylococcal resistance to penicillin at this period was 17 %, by 1952, during the Korean War, it had reached two-thirds of the strains isolated from wounded soldiers. The first reports of enterobacteria producing New Delhi (NDM) metallo-beta-lactamase in war wounds were documented during the Libyan conflict. During the military operations conducted by the coalition forces in Iran and Afghanistan, carbapenem-resistant *A. baumannii* swiftly emerged as a prominent threat, becoming a prevalent cause of serious wound infections [3,4,5]. This phenomenon can be explained by the fact that, in wartime, the urgent need for daily empirical use of antibiotics in large numbers of wounded patients exerts rapid and powerful selective pressure on wound microflora. Concurrently, nosocomial transmission plays a critical role in the dissemination of these resistant bacterial strains, as the need for rapid decision-making concerning treatment choices, aimed at the preservation of life, often supersedes infection control measures.

The full-scale Russian – Ukrainian war is no exception in this regard. The microflora of combat wounds and the antibiotic resistance profiles of wound pathogens have been monitored from the onset of hostilities in eastern Ukraine in 2014 to the present [6]. The findings provide compelling evidence of a strong association between the proliferation of antibiotic-resistant bacterial pathogens and armed conflicts.

Aim

The aim of the study was to identify the dominant clonal lineages of pathogens causing combat wounds and to determine their antimicrobial resistance determinants for the purpose of optimizing antimicrobial drug administration in wartime.

Materials and methods

A bacteriological study of the wound contents of wounded patients who were treated in hospitals in the Central region between March 2022 and September 2023 to receive specialized and highly specialized medical care was conducted. For comparison, we used bacteriological data obtained prior to the full-scale invasion, during the Anti-Terrorist Operation / Joint Forces Operation (ATO / JFO) period from 2014 to 2020.

Whole genome sequencing using Illumina MiSeq and NextSeq instruments and subsequent molecular analysis were performed in the USA at the Multidrug-resistant Organism Repository and Surveillance Network (MRSN) laboratory, as previously described [7,8,9].

Antibiotic sensitivity was tested using the disc diffusion method in accordance with the European Committee on Antimicrobial Susceptibility Testing (EUCAST) recommendations. Antibiotic resistance profiles were assessed according to the criteria established by A. P. Magiorakos et al. [10].

Results

The results of bacteriological studies of 171 wounded soldiers with similar injuries in 2022–2023 confirmed the dominance of non-fermenting Gram-negative microorganisms. The species composition of wound pathogens underwent a slight alteration, with an increase in the prevalence of representatives of the *Enterobacteriaceae* family (Fig. 1).

The results of our investigations have shown a significant increase in the frequency of *K. pneumoniae* isolation. The findings of this study corroborate this trend, as the frequency of this bacterial species isolation has increased to 20.7 % compared to 8.6 % prior to the commencement of the full-scale war. Among other *Enterobacteriaceae* found in wound contents, *E. coli* was identified in 9.1 % of cases, and *Enterobacter* spp. in 6.2 %. Among non-fermenting Gram-negative bacteria, the frequency of *A. baumannii* isolation has increased from 29.6 % to 35.7 % in the last period, but *P. aeruginosa* has become much less common (from 29.6 % to 14.9 %). The proportion of Gram-positive cocci was low, and they were most often represented (5.8 %) by *Enterococcus* spp.

In assessing the phenotypic resistance profiles of the most prevalent wound pathogens, a predominance of multidrug-resistant (MDR) strains was observed, with 95.6 % of *A. baumannii* isolates falling into this category. Notably, 41.1 % of these MDR strains demonstrated an extensive degree of resistance, designated as extensively drug-resistant (XDR). The molecular genetic analysis carried out on the *A. baumannii* isolates revealed the presence of eight distinct clonal lineages. The presence of such genetic diversity was indicative of the multi-locality of *Acinetobacter* sources in Ukraine.

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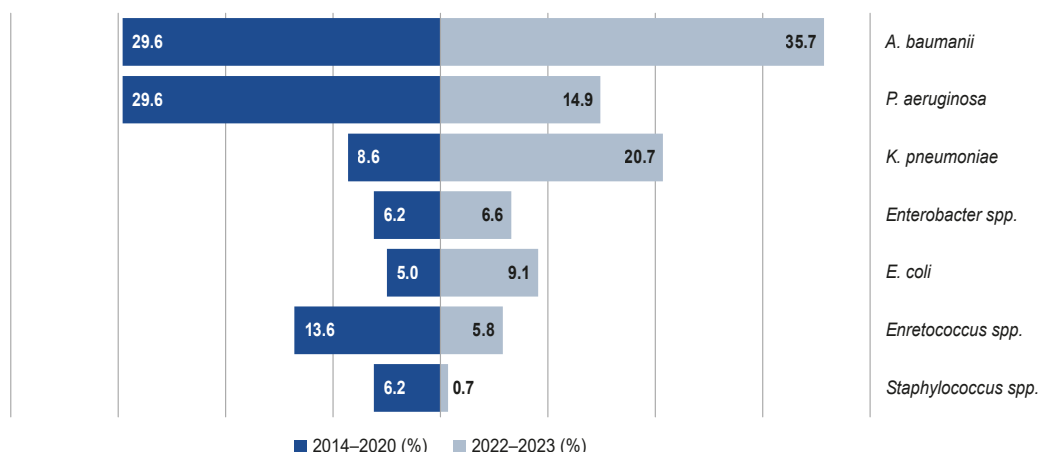


Fig. 1. Pathogen Spectrum in Combat Wound Infections, Ukraine (2014–2020 vs. 2022–2023). Values indicate the proportion of isolates from combat wound infections in each period.

Representatives of high-risk international clones (ICs), which are carriers of genetic determinants of resistance to antibiotics of various classes, represent a large proportion of isolated cultures. Consequently, 17.6 % of the *A. baumannii* belonged to the world's most widespread high-risk clonal line ST2, and carried the carbapenemases *bla*_{OXA-23}, *bla*_{OXA-72}, and 16S methyltransferase gene, *armA*, providing resistance to all clinically relevant aminoglycosides. From 2014–2022, a single case of *A. baumannii* ST2 was isolated; in contrast, from 2022–2023, 12 of the 68 isolated strains belonged to this sequence type. This finding indicates the intra-hospital and inter-hospital spread of pathogens. The presence of genetically related isolates of this sequence type, with no more than 10 single nucleotide differences in the genome, in three hospitals in Vinnytsia, suggests that these patients were in the same medical facility at the previous stage of medical evacuation.

The phenotypic resistance exhibited by isolates of this sequence type demonstrated a complete congruency with their genotype. In the present study, seven isolates have been found to carry the carbapenemase gene, *bla*_{OXA-23}, and the *armA* 16S methyltransferase gene, therefore, they were resistant to β -lactams and aminoglycosides retaining susceptibility to colistin. In contrast, one isolate, which carried the *bla*_{OXA-72} carbapenemase gene but lacked methyltransferase activity, demonstrated sensitivity to colistin and tobramycin. The remaining isolates, devoid of carbapenemase and methyltransferase genes, exhibited MDR and sensitivity to colistin, aminoglycosides, and carbapenems.

It is noteworthy that 23 (33.8 %) strains of *A. baumannii* are assigned to the globally prevalent clone lineage ST78 and its single locus variant (SLV) ST1077. Prior to 2022, isolates of clone ST78 often were identified in the cultures of wounded patients in Ukraine. The 12 isolates obtained from three hospitals in Vinnytsia following 2022 formed a cluster of genetically highly similar isolates, differing by 1–18 single-nucleotide differences. All isolates were found to be carriers of the *bla*_{OXA-72} carbapenemase gene, and nine of these additionally carried the *armA* gene. The isolates exhibited phenotypic sensitivity to colistin.

The most prevalent clone identified in our studies (17 isolates, 25 % of the total) was the clonal group ST19, which has not been included in the list of high-risk international clones being a carrier of carbapenemase genes. Five isolates were identified as carrying the *bla*_{OXA-23} gene, whereas 11 isolates were determined to harbor the *bla*_{OXA-72}. In the absence of 16S methyltransferase genes, all representatives exhibited sensitivity to gentamicin and tobramycin, in addition to colistin.

The representation of the high-risk clonal lines among the *P. aeruginosa* isolates obtained was not significant. A total of 40 bacterial isolates were taken, including three isolates of ST235 (7.5 % of the total) and one isolate of ST357 (2.5 %).

A considerably higher frequency of two other clones was observed: ST773 (13 isolates, 32.5 %) and ST1047 (10 isolates, 25 %). Moreover, all recently recovered isolates have been found to be genetically closely related (≤ 10 single-nucleotide polymorphisms) to one isolate obtained in 2019 from a wounded patient treated in a medical facility in Kyiv. All isolates of this clonal line were resistant to fluoroquinolones and imipenem. Resistance to cephalosporin antibiotics, aminoglycosides, and meropenem has been found in 69.2 % of isolates of this clone. The only PDR isolate identified in this study that was resistant to colistin belonged to this clone. At the same time, three strains (23.1 % of *P. aeruginosa* ST773 isolates) belonged to the non-MDR (nMDR) group.

Among the ST773 isolates, four genetically related isolates had a set of two metal-beta-lactamase genes, *bla*_{NDM-1} and *bla*_{IMP-1}, as well as 16S rRNA methyltransferase *mtB4*. Another six isolates carried *bla*_{NDM-1}, and the *mtB4* 16S methyltransferase gene. Phenotypic sensitivity to antibiotics was consistent with the carriage of genetic markers, as the nMDR isolates did not carry the genes for carbapenemase and 16S RMTases production, and their resistance to fluoroquinolones was due to the *qnr VC1* gene, and mutations in the *gyrA* and *parC* genes.

Of the ten ST1047 isolates obtained in this study, eight were isolated from patients in different departments of the same hospital. Two of them were isolated from burn

wounds, three from festering mine-blast wounds, and three from the respiratory tract of intensive care unit patients with signs of ventilator-associated pneumonia. Regardless of the department in which the patient was treated and the location of the sample collection, the isolates were highly genetically related (0–1 allelic differences) suggesting nosocomial transmission. All isolates of this clonal line belonged to the XDR phenotype and were resistant to all antibiotics regulated by EUCAST for *P. aeruginosa*, except for colistin. It should be noted that all of them were also sensitive to cefiderocol, which is currently unavailable in Ukraine. Among the important genetic determinants of resistance in all isolates of this clone is imipenemase *bla*_{IMP-1}.

The 56 isolates of *K. pneumoniae* belonged to five clonal groups, and one isolate was classified as ST15. The largest group was represented by the relatively young, high-risk ST395 clone, identified in France in 2010, consisting of 20 isolates (35.7 %). The second most common group was the long-known high-risk international clone ST307, which consisted of 14 isolates (25.0 %). The globally widespread clone ST147 accounted for 17.9 % (10 isolates). Among the remaining isolates, 14.3 % (8 isolates) belonged to ST39, and 5.4 % (3 isolates) belonged to ST23. In terms of phenotypic sensitivity, isolates of the most common sequence type ST-395 were divided into MDR – 55 % and XDR – 45 %. 60 % of isolates of this sequence type retained sensitivity to at least one aminoglycoside antibiotic, 50 % to ceftazidime/avibactam, and 50 % to tigecycline. Sensitivity to other antibiotics was lower. Only one of the 20 isolates did not carry carbapenemase genes, while the rest carried the class D beta-lactamase gene *bla*_{OXA-48} or *bla*_{NDM-1}. All strains of this clone carried the *bla*_{CTX-M-15} extended-spectrum beta-lactamase gene. Only one isolate had no genetic markers of hypervirulence, while the rest carried one or a combination of the yersiniabactin (*ybt*), mucoid factor (*rmpA*) and aeroblastin (*iuc*) loci.

Fighting in Ukraine has been going on for over 10 years, but before the full-scale war started in 2022, *K. pneumoniae* ST-307 was not found in wounded soldiers. Based on phenotypic sensitivity, isolates were divided in half: 50 % (n = 7) – MDR, 50 % (n = 7) – XDR. Extended-resistance variants were sensitive to colistin (n = 4) or to colistin and tigecycline (n = 3), while MDR variants were also sensitive to ceftazidime/avibactam, amikacin, meropenem and imipenem. In the genome, 8 of 14 isolates had the carbapenemase determinant *bla*_{NDM-1}, and only one of them retained sensitivity to meropenem and imipenem. 6 other isolates did not carry carbapenemases and were phenotypically sensitive to carbapenems. 9 isolates carried the 16S RMTase *armA* and were phenotypically resistant to aminoglycosides. Among the hypervirulence markers, 4 isolates of this clone had a combination of aeroblastin, yersiniabactin and *rmpA* mucus regulator genes, 5 isolates had *aeroblastin* and *yersiniabactin*, and the rest had only the *yersiniabactin* gene.

We also have not detected any isolates of another international high-risk clone, *K. pneumoniae* ST147, before 2022. 7 of the 10 isolates of this lineage obtained recently belonged to XDR in terms of phenotypic sensitivity and were sensitive only to colistin and amikacin or gentamicin.

All 10 isolates carried carbapenemase: 3 isolates carried *bla*_{NDM-1}, 3 isolates carried *bla*_{OXA-48}, and the remaining

4 isolates carried both. Only *bla*_{OXA-48} carriers showed phenotypic sensitivity to cephalosporins and imipenem/cilastatin. Only 1 isolate carried the 16S rRNA methyltransferase *armA*, while the rest of the isolates were resistant to aminoglycosides and fluoroquinolones due to the genetic loci of aminoglycoside acyltransferases (*aac*(6')-Ib-AKT), the RND efflux pump gene *oqxA*, and mutations in the *gyrA* and *parC* genes. Among the ST-147 isolates, 9 carried *aerobactin* and *yersiniabactin* locus, one isolate had only the *aerobactin* locus.

Discussion

The war in Ukraine has led to the emergence of a potentially hazardous reservoir of high-risk clones of antibiotic-resistant wound pathogens. A study of combat wounds to the limbs and soft tissues of the torso in 161 wounded soldiers between 2014 and 2020 revealed that the dominant wound microflora was non-fermenting Gram-negative bacteria, namely *A. baumannii* and *P. aeruginosa*, in tandem with members of the *Enterobacteriaceae*. In the initial phase, the total proportion of these bacteria constituted 80.2 % of the total number of isolated strains. However, following the full-scale invasion, this proportion increased to 93.5 % [11].

It is known that on the European continent, representatives of two clonal lines dominate among medical isolates of *A. baumannii*: IC I and IC II (ST19, ST2) [12]. Our findings support this concept, as the combined proportion of isolates belonging to these two clonal lineages among the strains, we retrieved accounted for 45.5 %. Particular attention should be drawn to the prevalence of the *Acinetobacter* clone IC Y1, which constituted 33.8 % of the isolates and was uniformly classified as MDR or XDR. The ST78 is categorized as an International Clone 6 (IC6), and it is designated as the “Italian clone” because it was first isolated in Italy during the mid-2000s [13].

The European Society of Clinical Microbiology and Infectious Diseases has identified 10 high-risk clonal lines of *P. aeruginosa* that are globally widespread and carry genetic determinants to produce extended-spectrum beta-lactamases of classes A and D (*bla*_{CTX-M-15}, *bla*_{KPC}, *bla*_{GES}, *bla*_{OXA}), metallo-beta-lactamases (*bla*_{VIM}, *bla*_{IMP}, *bla*_{NDM}), and 16S rRNA methylases *rmtB4*. The following list, arranged in order of significance: ST235, ST111, ST233, ST244, ST357, ST308, ST175, ST277, ST654, ST298 [14]. Before 2022, ST235 isolates had not been documented in patients from the hospitals included in this study, although they had been reported in other regions of Ukraine [7]. In one hospital, three genetically related ST235 isolates were identified, two from burn wounds and one from a gunshot wound. All isolates exhibited an XDR phenotype. In addition to susceptibility to colistin, they demonstrated sensitivity to ceftazidime / avibactam. Genomic analysis revealed the presence of ESBL determinants, including class A *bla*_{GES-1}. Before 2022, representatives of the high-risk clonal lineage ST357 had not been reported in the hospitals participating in this study. A single isolate detected during the present investigation demonstrated susceptibility only to colistin. *P. aeruginosa* ST773 lineage has long attracted attention due to its global dissemination and frequent association with metallo-β-lactamase production [15,16]. In our pre-

vious studies, ST773 had also been identified; however, its frequency of isolation increased after the onset of the full-scale war [17].

Between 2017 and 2024, *K. pneumoniae* moved from fifth to first place in the WHO list of bacteria with critically high priority due to antibiotic resistance [1], reflecting a global trend towards an increase in the proportion of this bacteria in the development of severe infections. Our data from 2022–2023 demonstrate a significant rise in *Klebsiella* isolation, supporting this trend. The clinical significance of *K. pneumoniae* is highlighted by the emergence and rapid spread of convergent pathotypes of this bacterial species, which, in addition to antibiotic resistance, carry molecular genetic markers of hypervirulence and pose a significant clinical threat [18,19].

Researchers from a number of foreign clinics have also reported on the threat of global spread of high-risk clones of wound pathogens since the beginning of the war in Ukraine [20]. As early as March 2023, German medical practitioners documented the isolation of *K. pneumoniae* ST147, ST307 and ST395, *A. baumannii* ST78, and *P. aeruginosa* ST1047 from wounded Ukrainian soldiers who had been evacuated to Germany for treatment [21]. In the Netherlands, a country with a low prevalence of multidrug-resistant bacteria, *K. pneumoniae* ST307, ST147 and ST395, *P. aeruginosa* ST1047 and ST773 were isolated from persons displaced from Ukraine. Comparable findings have been documented from Denmark and Poland [22,23].

To prevent the further spread of dangerous clones of wound pathogens, the European Centre for Disease Prevention and Control (ECDC) recommended preventive isolation and screening for the presence of multidrug-resistant bacteria in patients transferred from hospitals in Ukraine [24].

Conclusions

1. This study provides a comprehensive analysis of the antimicrobial resistance profiles and clonal population structure of bacterial pathogens isolated from combat wounds sustained during the war in Ukraine between 2014 and 2023.

2. Across this period, we documented a marked shift towards the predominance of multidrug-resistant and extensively drug-resistant Gram-negative organisms, with *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Klebsiella pneumoniae* as the principal etiological agents.

3. Whole-genome sequencing has revealed the emergence and dissemination of high-risk international clones, including *A. baumannii* ST2, ST78, and ST1077, *P. aeruginosa* ST235, ST357, ST773, and ST1047, and *K. pneumoniae* ST147, ST307, and ST395. Many of these lineages carried clinically significant resistance determinants, including *bla*_{OXA}-type carbapenemases, *bla*_{NDM} and 16S rRNA methyltransferases, in combination with markers of hypervirulence in *K. pneumoniae*.

Prospects for further research. Given the widespread prevalence of international high-risk clones of wound pathogens in medical facilities at the third and fourth stages of medical evacuation, it is essential to investigate their occurrence in healthcare facilities at earlier stages to identify

their reservoirs and sources of dissemination. Furthermore, a microbiological evaluation of the hospital environment in these institutions is necessary to elucidate the pathways and factors contributing to infection transmission.

Ethical approval

The Bioethics Committee of National Pirogov Memorial Medical University (Vinnytsia) examined the scientific study materials and confirmed their compliance with the basic bioethical norms of the Declaration of Helsinki adopted by the General Assembly of the World Medical Association, the Council of Europe Convention on Human Rights and Biomedicine (1977), the relevant provisions of the WHO, International Council of Medical Scientific Societies, International Code of Medical Ethics (1983), Council of Europe Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes of 18.03.1986, EEC Directive No. 609 of 24.11.1986 and Order of the Ministry of Health of Ukraine No. 281 of 01.11.2000. Protocol No. 7 of 09.09.2025.

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