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# Antimicrobial resistance of combat-related infections. Literature review

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The article compiles information from scientific reports published between 2011 and 2024, indexed in both Ukrainian and international databases. The studies focus on the microflora of combat wounds and the antimicrobial resistance of primary pathogens responsible for purulent-septic complications in patients from conflict zones. We analyzed the etiological structure of common wound infections and their antibiotic resistance in military personnel with combat-related soft tissue injuries who were evacuated from the combat zone in eastern Ukraine.

A systematic review of approaches to addressing infection prevention and infectious complications in patients with combat-related soft tissue injuries has demonstrated the rational and justified use of antibiotics, as well as adherence to infection control protocols in developed countries. These measures effectively reduce the risk of surgical site infections. Since March 2022, the war in Ukraine has led to significant population migration and the evacuation of numerous patients from Ukrainian hospitals to medical facilities within European Union. Multidrug-resistant strains have been identified in patients from Ukraine. According to data from Ukrainian military and civilian hospitals, multidrug-resistant strains were prevalent in Ukraine between 2014 and 2024. *Acinetobacter baumannii* exhibited the highest resistance rates, with 92.5 % of strains resistant to fluoroquinolones, 83.0 % to aminoglycosides, and 67.9 % to carbapenems. Resistance to carbapenems was observed in 55.6 % of *Pseudomonas aeruginosa*, 42.9 % of *Escherichia coli*, and 32.8 % of *Klebsiella pneumoniae*. Microbial resistance emerged more frequently in Ukrainian military hospitals than in civilian hospitals and European medical institutions. The study provides epidemiological data on multidrug-resistant microorganisms isolated from patients evacuated from the combat zone in eastern Ukraine. To improve treatment options for Gram-negative bacterial infections, it is essential to identify additional phenotypic resistance profiles of multidrug-resistant microorganisms, especially those resistant to new antibiotic combinations.

**Keywords**
microorganisms, infection, antibiotics, antibiotic resistance, combat-related injuries, armed conflict, Ukraine.

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Antimicrobial resistance (AMR) is the ability of microorganisms to resist the action of antibiotics to which they were previously sensitive. This capability allows microorganisms to survive and reproduce despite antibiotic treatment. Microorganisms can develop AMR through various mechanisms, including mutation, horizontal gene transfer, and efflux pumps [4]. Antibiotic resistance is a significant global health concern [27, 30], posing a serious threat by reducing the effectiveness of treatments, increasing morbidity, and leading to higher mortality rates [9]. The World Health Organization (WHO) recognizes AMR as one of the top ten major threats to global health, with an estimated 700,000 deaths occurring annually [45]. In 2019, 1.27 million deaths were attributable to AMR, surpassing the mortality associated with HIV/AIDS (864,000) and malaria (643,000) [40].

Furthermore, AMR prolongs hospital stays, causes disability due to infections [5], and increases economic costs. According to the World Bank, AMR could lead to additional healthcare expenditures of up to $1 trillion by 2050 and result in annual losses to gross domestic product (GDP) ranging from $1.0 to $3.4 trillion by 2030 [13].

Key priorities in combating AMR include preventing infections that could lead to the inappropriate use of antimicrobial agents, ensuring universal access to quality diagnostics and proper treatment of infections, and promoting strategic initiatives such as monitoring AMR and the consumption/use of antimicrobial agents. This also involves supporting research and development of new diagnostic tools and medicines [3]. Many diseases caused by antibiotic-resistant microorganisms underscore the urgent need for new prevention methods.

The ongoing conflict in Ukraine has exerted unprecedented pressure on the region's medical infrastructure and healthcare services [22, 25]. Following the full-scale invasion by Russian troops, the Ukrainian armed forces established efficient evacuation routes for wounded soldiers from the battlefield, drawing on both their own innovations and the experience of foreign medical services. Most injuries involve soft tissues of the torso and limbs. At all stages of evacuation and medical treatment, there is a significant risk of wound infection, which can complicate healing and pose a threat of infectious comorbidities.

It is well-known that gunshot wounds are associated with a high level of microbial contamination, particularly with opportunistic pathogens (OPs), which predispose patients to purulent-inflammatory infections. Given that a considerable number of wounded individuals develop infectious complications caused by multidrug-resistant strains of OPs, an urgent issue arises regarding appropriate antibiotic therapy and prophylaxis of these infections. The spectrum of microorganisms isolated from combat-related gunshot and mine-explosive wounds is continuously evolving. Understanding the predominant infections and their resistance to antimicrobial agents is crucial for effective patient management. However, in the existing national literature, the issue of antimicrobial resistance (AMR) in combat-related infections causing purulent-inflammatory complications is insufficiently addressed.

**Objective** – to analyze data on the antibiotic resistance of primary combat-related infections in patients with soft tissue injuries evacuated from the zone of armed conflict in eastern Ukraine.

## Materials and methods

A review of scientific reports published between 2011 and 2024 was conducted. The databases used in this study included PubMed, MEDLINE, and Cochrane, as well as the National Scientific Medical Library of Ukraine, the National Library of Ukraine named after V. I. Vernadsky, and the library of Bogomolets National Medical University. To find relevant materials, the following keywords were used: «antibiotics», «antibiotic resistance», «microorganisms», «infected combat-related injuries», «armed conflict», and «Ukraine».

## Results and discussion

A total of 150 national and international scientific reports were reviewed, of which 46 met the criteria of our study. The analysis revealed significant differences in the etiology of wound infections and antibiotic resistance indicators, which varied depending on the timing and conditions of medical assistance provided at different stages of evacuating wounded military personnel. The battlefield presents serious challenges for the treatment of combat-related injuries, including frequent relocations of patients between facilities and medical teams, limited supplies in the combat zone, and difficulties encountered during long-distance medical evacuations [1, 2, 7].

The fundamental principle of military surgery is that any gunshot wound is considered microbiologically contaminated. Such wounds invariably contain mixed microbial flora, including OPs, as well as necrotic tissue foci, creating a favorable environment for the development of infectious and purulent-inflammatory conditions. WHO data indicate that 44–61 % of wounded individuals develop infectious complications [26]. In Ukraine, purulent-septic complications in gunshot wounds occurred in 50–75 % of cases [1, 2, 7], with a significant proportion of these infections caused by multidrug-resistant strains of OPs. A. Salmanov et al. [21] conducted a prospective multicenter study across 17 regional hospitals in Ukraine between 2019 and 2021, detecting surgical site infections in 15.3 % of patients. The main causative agents of these infections were *Escherichia coli* (21.3 %), *Enterobacter* spp. (12.9 %), *Klebsiella pneumoniae* (10.8 %), *Staphylococcus aureus* (9.1 %), and *Pseudomonas aeruginosa* (8.1 %), followed by *Enterococcus* spp. (7.3 %), *Proteus mirabilis* (6.8 %), *Acinetobacter baumannii* (6.1 %), Stenotrophomonas maltophilia (5.7 %), Serratia marcescens (5.3 %), and other microorganisms. Overall, 85.1 % of strains isolated from patients with infectious complications were multidrug-resistant. Methicillin resistance was identified in 41.2 % of *S. aureus* isolates (MRSA), resistance to vancomycin in 11.8 % of enterococci, resistance to third-generation cephalosporins in 48.4 % of all *Enterobacteriaceae*, and resistance to antimicrobials such as carbapenems in 71.3 % of all non-fermenting Gram-negative bacilli. Additionally, 25.1 % of the tested isolates were classified as multidrug-resistant. This study demonstrated that most hospitals are contaminated with multidrug-resistant hospital strains of OPs. A significant proportion of infectious complications among patients is associated with various factors, primarily the medical personnel, who can facilitate the transmission of resistant strains within healthcare institutions [34, 35], as well as prolonged medical evacuation of the wounded individuals.

In 2019, M. D. Zheliba et al. [1] conducted a study on the microbial landscape of combat wounds. The research was based on examinations and treatment of 262 victims of combat actions in eastern Ukraine, who received care at the Military Medical Clinical Center of the Central Region (Vinnytsia). Patients were admitted to the clinic 3–20 days after sustaining injuries. Throughout the evacuation process, all victims underwent surgical wound treatment and received antibiotics. Wound material was collected for microbiological examination on the day of hospitalization and during ongoing treatment. Microbiological analysis of biological material from the wounds revealed a predominance of Gram-negative non-fermenting OPs among bacterial cultures of gunshot wounds (68 %), with *Acinetobacter* spp. accounting for 53 % of cases and *Pseudomonas* spp. for 15 %. Most of these strains (79.5 %) were multidrug-resistant. Gram-positive OPs were represented by *Enterococcus* (10 %) and *Staphylococcus* (14 %). Staphylococci prevailed (36.8 %) within the wound microflora during the first week after injury. Gram-negative OPs were isolated in 21.1 % of cases. During the second week after injury, Gram-negative OPs became predominant. Between the second and fourth weeks, OP associations comprised *Acinetobacter*ia and *Klebsiella* or non-fermenting bacilli and enterococci. The majority (79.5 %) of strains exhibited multidrug resistance. The highest resistance levels were observed in strains of Gram-negative non-fermenting OPs. *Acinetobacter* spp. strains were resistant to most tested antibiotics but remained sensitive to polymyxin B and colistin. *P. aeruginosa* strains showed high antibiotic resistance (75 %). All isolates of *Enterobacteriaceae* demonstrated 100 % resistance to various generations of cephalosporins, penicillins, and fluoroquinolones. These strains were sensitive to amikacin, cefoperazone-sulbactam, and colistin, with moderate resistance observed to meropenem.

V. Kondratyuk et al. [25] conducted a microbiological study in four Ukrainian military hospitals from 2014 to 2020. A total of 813 microorganisms isolated from 162 patients were analyzed. All identified strains (*Acinetobacter baumannii*, *Pseudomonas aeruginosa*, *Escherichia coli*, and *Klebsiella pneumoniae*) belonged to Gram-negative OPs. *A. baumannii* strains (92.5 %) demonstrated the highest antimicrobial resistance level. Specifically, resistance was observed against fluoroquinolones (83.0 %), aminoglycosides (70.2 %), and carbapenems (67.9 %). In contrast, resistance to carbapenems was 55.6 % in *Pseudomonas aeruginosa*, 42.9 % in *Escherichia coli*, and 32.8 % in *Klebsiella pneumoniae*. Multidrug-resistant strains carried numerous antibiotic-resistant genes. *K. pneumoniae* co-produced class A and D β-lactamases, with one case producing blaNDM-1 and rmtC 16S rRNA methyltransferase. *A. baumannii* produced class A and D β-lactamases but did not produce metallo-β-lactamases. *P. aeruginosa* contained a wide range of β-lactamases from classes A and D, along with metallo-β-lactamases. Gram-positive cocci were susceptible to the tested antibiotics.

Additionally, research was carried out at the Communal Non-Profit Enterprise «Specialized Multidisciplinary Clinical Hospital of Kyiv». *K. pneumoniae*, *Pseudomonas aeruginosa*, and *Acinetobacter baumannii* were the primary pathogenic strains that caused substantial concerns regarding antibiotic resistance, particularly resistance to reserve antibiotics [11].

Before the large-scale conflict in 2022, Ukraine provided surveillance data to the Central Asia and Europe antimicrobial resistance monitoring network, which indicated an increase in the prevalence of multidrug-resistant strains of OPs (https://apps.who.int/iris/rest/bitstreams/1496762/retrieve). This rise was especially notable among military personnel, likely due to the irrational use of antimicrobial agents and limited possibilities for prevention and control in the treatment of affected individuals after the annexation of Ukrainian regions by Russia in 2014 [25].

Previous reports from eastern Ukraine documented cases of infections caused by multidrug-resistant strains of OPs, including *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacterales*, during the hospitalization of individuals with combat-related injuries [25]. These strains encompassed various clonal lineages, many of which carried carbapenemases, extended-spectrum β-lactamases (ESBLs), and 16S methyltransferases [18]. A total of 32 *A. baumannii* isolates resistant to carbapenems and fluoroquinolones were obtained from patients with combat-related injuries sustained during the conflict in eastern Ukraine and treated in Bundeswehr hospitals in 2014 and 2015 [18].

More than a decade ago, resistant or even multidrug-resistant *A. baumannii* was described as a significant concern among patients with combat-related injuries [12, 33]. It remains a relevant issue today [10, 29, 38]. Typically, nosocomial (hospital-acquired) transmission is more likely in patients with combat wounds than auto-infection, due to prior colonization of *A. baumannii* [23, 39], with minimal or no impact from antimicrobial agents on the injury site [32]. Most international reports of *A. baumannii* infections related to war are associated with armed conflicts in Iraq [21, 31, 46] and Afghanistan [19, 46]. Since the onset of the armed conflict in eastern Ukraine, cases of infectious complications caused by multidrug-resistant *Acinetobacter* spp. have been reported [42]. However, no studies have yet been conducted on species distribution. *Acinetobacter* spp. were particularly prevalent in wound flora during the later stages of wound consolidation, while Gram-positive bacilli dominated during the initial phase [42]. According to a multicenter study of Ukrainian hospitals conducted between 2013 and 2015, carbapenem resistance in *A. baumannii* isolates from blood samples is substantial, with a prevalence of 63.2 % [37].

A recent study revealed that 78.6 % of *A. baumannii* isolates causing healthcare-associated infections in intensive care units in Ukraine were resistant to carbapenems [36]. This poses a significant challenge for antimicrobial therapy. Ukrainian doctors have reported attempting desperate therapeutic measures, including the use of doxycycline, in cases of *A. baumannii* resistant to aminoglycosides. Furthermore, existing data on the primary mechanisms of carbapenem resistance in Ukraine remain limited, with most research focusing on *Enterobacteriaceae* rather than non-fermenting bacilli such as *A. baumannii* [20, 29].

H. Granzer et al. [17] detailed the epidemiology of carbapenem- and fluoroquinolone-resistant *A. baumannii* isolates obtained from patients with injuries sustained during the armed conflict in eastern Ukraine. These patients were treated in Bundeswehr hospitals in Berlin, Hamburg, Koblenz, and Ulm between 2014 and 2015. A total of 32 *A. baumannii* isolates resistant to carbapenems and fluoroquinolones were collected from 21 patients. Polymerase chain reaction (PCR) analysis revealed colonization or infection with multiple clones in some patients, indicating a high colonization pressure.

R. D. Zwittink et al. [47] reported the emergence of multidrug-resistant microorganisms in patients from Ukraine who have received treatment in the Netherlands since March 2022. The study included 58 patients and 75 isolates. Approximately half of these patients had been recently hospitalized in Ukraine. Genomic surveillance indicated that most multidrug-resistant strains of OPs belonged to widespread epidemic lineages found worldwide. Notably, 60 % of these strains carried genes for metallo-β-lactamases (NDM) from New Delhi. Healthcare specialists should be aware of the increasing spread of such multidrug-resistant OP strains, which are associated with the medical evacuation of wounded individuals from Ukrainian hospitals to medical facilities within the European Union, particularly the Netherlands [15]. The European Centre for Disease Prevention and Control (ECDC) recommends preemptive isolation of patients transferred from Ukrainian hospitals or those with a history of hospitalization in Ukraine within the past 12 months. Additionally, screening for multidrug-resistant OP strains is advised [14]. In Dutch hospitals, the primary multidrug-resistant pathogens causing purulent-inflammatory infections of gunshot wounds in admitted patients included *A. baumannii*, *E. cloacae*, *E. coli*, *K. pneumoniae*, *Proteus mirabilis*, *Providencia stuartii*, and *P. aeruginosa*.

According to WHO data, information collected from Ukrainian military and civilian hospitals indicates a high prevalence of multidrug-resistant microorganisms in Ukraine from 2014 to 2021 [25, 35, 44]. Reports have shown resistance rates of 17–84 % to third-generation cephalosporins and carbapenems among *Enterobacterales* and *P. aeruginosa*, as well as over 50 % to carbapenems, fluoroquinolones, and aminoglycosides among *Acinetobacter* species [25, 35, 44]. European surveillance data for Ukraine indicate that 18 % of *S. aureus* strains are MRSA, with 41 % of methicillin-resistant strains associated with *S. aureus* infections related to healthcare settings [35, 44]. The multidrug-resistant strain of *A. baumannii* was recognized as a significant problem among US military personnel with combat-related injuries sustained in Afghanistan and Iraq in 2004. Similarly, in the UK, imported multidrug-resistant *A. baumannii* strains from Iraq and Afghanistan were identified as a potential source of severe hospital-acquired infections. The ability of *A. baumannii* to rapidly develop resistance to multiple classes of antibiotics has increased awareness of its clinical significance for hospital infections [24, 33].

A high prevalence of colonization was also observed among military personnel and civilian war victims transferred from Libya to German hospitals, notably a high frequency of multidrug-resistant strains of OPs [28]. Among 67 patients transferred during 2016–2017, MRSA and multidrug-resistant OPs were documented in 16 % and 60 %, respectively, with 37 isolates producing carbapenemases (such as New Delhi metallo-β-lactamase (NDM), (OXA)-48 : 15, OXA-23 : 9) [28].

Carbapenemases are β-lactamases, enzymes that often confer resistance to antimicrobial agents, particularly last-line antibiotics [28]. Among war victims in Syria requiring surgical intervention during 2011–2013, invasive surgical site infections involved 69 % of cases with highly resistant strains of *A. baumannii*, *E. coli* producing extended-spectrum β-lactamases (ESBL), and MRSA [41]. Studies conducted in Syria, neighboring countries, and European hospitals have found an increase in the number of carriers of multidrug-resistant microorganisms (MDRO), including *Enterobacterales* producing ESBL or NDM enzymes, and multidrug-resistant strains of *A. baumannii* in 33–83 % of individuals [8].

Observations conducted during the war in Afghanistan (1979–1989) demonstrated contamination of gunshot wounds with Gram-positive aerobic microflora, spore-forming bacilli, *Clostridia*, non-spore-forming anaerobes, and coagulase-positive staphylococci from the moment of injury. Delays in evacuation or medical aid were associated with a shift in microflora towards Gram-negative bacilli. The microbiology of combat wounds sustained during US military operations in Iraq and Afghanistan (2001–2014) indicates a dominance of multidrug-resistant bacteria among wound pathogens. Specifically, this includes *A. baumannii*, *Enterobacteriaceae* such as *K. pneumoniae* and *E. coli*, which produce broad-spectrum β-lactamases, and MRSA [6]. Similar patterns were observed during the wars in Libya and Syria in 2011 and 2012, respectively. Combat-related injuries predominantly revealed Gram-negative non-fermenting bacilli and *Enterobacteriaceae*, with isolated strains exhibiting multidrug resistance to most antibiotics [16]. These findings support the presence of distinct bacteriological patterns related to changes in combat wounds.

## Conclusions

Our research provided epidemiological data on multidrug-resistant microorganisms isolated from patients evacuated from the combat zone in eastern Ukraine. Additional phenotypic resistance profiles of multidrug-resistant microorganisms, particularly to new combinations of antibiotics, must be identified to expand therapeutic options for treating infections caused by Gram-negative bacilli.

To further elucidate these findings, it is necessary to conduct studies on the local epidemiology of antimicrobial-resistant pathogens responsible for purulent-inflammatory complications related to the medical care of wounded military personnel at various stages of evacuation.

### Declaration of interests

The author declares no conflicts of interest.

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# Антимікробна резистентність збудників інфекцій бойових травм. Огляд літератури

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Стаття узагальнює дані наукових статей, опублікованих у період з 2011 до 2024 р. та індексованих в Україні й міжнародних базах даних, щодо мікрофлори бойових ран і антимікробної резистентності основних патогенів гнійно-септичних ускладнень лікування пацієнтів із зон збройних конфліктів. Проаналізовано етіологічну структуру основних збудників ранових інфекцій та їхню антибіотикорезистентність у військовиків із бойовими травмами м'яких тканин, евакуйованих із зони воєнного конфлікту на сході України.

Систематизація літературних джерел та підходів до вирішення проблеми профілактики інфікування пацієнта та лікування інфекційних ускладнень пацієнтів із бойовими травмами м'яких тканин виявила раціональне та обґрунтоване застосування антибіотиків у розвинених країнах і дотримання вимог інфекційного контролю, що сприяє мінімізації ризиків розвитку інфекцій ділянки хірургічного втручання. Починаючи з березня 2022 р., війна в Україні призвела до міграції частини населення та медичної евакуації великої кількості пацієнтів з вітчизняних лікарень до лікарень країн Європейського Союзу. У цих країнах спостерігалися випадки виділення мультирезистентних штамів у пацієнтів з України. Інформація, отримана з українських військових і цивільних шпиталів, свідчить про велику поширеність мультирезистентних штамів в Україні в 2014—2024 рр. Найвища резистентність виявлена в *Acinetobacter baumannii*: 92,5 % штамів були резистентними до фторхінолонів, 83,0 % — до аміноглікозидів, 67,9 % — до карбапенемів. У *Pseudomonas aeruginosa* резистентність до карбапенемів становила 55,6 %, у *Escherichia coli* — 42,9 %, у *Klebsiella pneumoniae* — 32,8 %. Частота виникнення резистентності серед досліджуваних патогенів в українських військових шпиталях була вищою, ніж у цивільних лікарнях та лікарнях європейських країн. Проведене дослідження дало змогу отримати епідеміологічну інформацію про організми з множинною лікарською стійкістю, виділені від пацієнтів зі східноукраїнської кризової зони. Необхідно визначити додаткові фенотипові моделі резистентності організмів із множинною лікарською стійкістю, зокрема до нових комбінацій антибіотиків, щоб розробити терапевтичні варіанти лікування інфекцій, спричинених грамнегативними бактеріями.

**Ключові слова:** мікроорганізми, інфекція, антибіотики, антибіотикорезистентність, бойові травми, збройний конфлікт, Україна.

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