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Characterization of wound infections among patients injured during the Ruso-Ukrainian war in a Role 4 hospital



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ABSTRACT

Introduction: The management of infections in war wounds is a problem aggravated by the presence of multiresistant bacteria and requires a combined approach with surgery. Literature has identified the risks and patterns of antibiotic resistance in previous armed conflicts, but the Russian-Ukrainian conflict has required the study of specific bacterial resistance patterns.

Methods: We included war-injured patients from the Russian-Ukrainian conflict transferred for treatment to the General Defense Hospital of Zaragoza from May 2022 to October 2023. Epidemiological data, factors related to the injury, presence of infection and microbiological results were collected; These data were subsequently analyzed statistically.

Results: Fifty-three patients were included in the study, with a mean age of 35.6 years; 83% were injured by an explosive mechanism and all received antibiotic therapy prior to transfer. Seventeen patients had skin, soft tissue or joint infection. Correlation was demonstrated with the presence of bone lesion (p 0.03), skin coverage defect (p 0.000) and presence of foreign bodies (p 0.006). Nine patients had monomicrobial cultures, and the most frequently isolated microorganisms were Gram negative bacilli (GNB) and *Staphylococcus aureus*. Virtually all GNB presented some resistance mechanism.

Conclusion: Our work shows the correlation of war wound infection with the presence of foreign bodies and affected tissues. Likewise, the presence of polymicrobial wounds is emphasized, with a predominance of GNB and multidrug-resistant *S. aureus*.

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Caracterización de las infecciones de herida entre pacientes procedentes de la guerra ruso-ucraniana en un hospital Role 4

RESUMEN

Introducción: El manejo de infecciones en heridas de guerra es un problema agravado por la presencia de bacterias multirresistentes y requiere de abordaje combinado con cirugía. La literatura ha identificado los riesgos y patrones de resistencia antibiótica en conflictos armados previos, pero el conflicto ruso-ucraniano ha precisado el estudio de patrones de resistencia bacteriana específicos.

Métodos: Se incluyeron los pacientes heridos de guerra del conflicto ruso-ucraniano trasladados para tratamiento al Hospital General de la Defensa de Zaragoza desde mayo de 2022 hasta octubre de 2023. Se recogieron datos epidemiológicos, factores relacionados con la lesión, presencia de infección y resultados microbiológicos; dichos datos posteriormente fueron analizados estadísticamente.

Palabras clave:

Infección de heridas
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Resultados: Se incluyeron 53 pacientes en el estudio, con una edad media de 35,6 años; el 83% fue herido por mecanismo explosivo y todos recibieron antibioterapia previa a su traslado. De ellos, 17 presentaron infección de piel y partes blandas o articular. Se demostró asociación con la presencia de lesión ósea (p 0,03), defecto de cobertura cutánea (p 0,000) y presencia de cuerpos extraños (p 0,006). 9 pacientes presentaron cultivos monomicrobianos, y los microorganismos más frecuentemente aislados fueron bacilos Gram negativos (BGN) y *Staphylococcus aureus*. Prácticamente todos los BGN presentaron algún mecanismo de resistencia.

Conclusión: Nuestro trabajo muestra la correlación de la infección de herida bélica con la presencia de cuerpos extraños y los tejidos afectados. Asimismo, se enfatiza la presencia de heridas polimicrobianas, con predominio de BGN y *S. aureus* multirresistentes.

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Introduction

Infection is an inherent problem with war wounds. With the advent of modern high-energy weapons, over the past century this problem has been exacerbated. These infections require meticulous treatment combined with surgery. Although the initial management of war-related injuries may be similar to other types of severe trauma, there are major differences in the definitive care of these patients, among which are the initial and systematic administration of broad-spectrum antibiotic therapy.¹

One of the most characteristic factors of combat-related wound infections is the causative pathogens. These wounds can be a major breeding ground for multidrug-resistant bacteria. The military literature systematically refers to the risks and patterns of antibiotic resistance in infections in soldiers caused by weapons of war.^{2–4} Although this distinctive feature has attracted attention, the fortunate lack of armed conflicts in Western countries in the last twenty to thirty years means there has been little characterisation of these pathogens in the literature corresponding to this period. Much of the existing literature tends to refer to conflicts in which the United States has intervened and in which soldiers were evacuated early to the hospitals where definitive care was to be provided.² In recent years, the literature has also referred to the risks associated with antibiotic resistance in conflicts in the Middle East and, more recently, in Ukraine.^{5,6} The literature has begun to identify the main factors that contribute to the emergence and spread of antibiotic resistance.^{7,8}

Since May 2022, the Hospital General de la Defensa de Zaragoza [Zaragoza General Hospital of the Defence] in Spain has been caring for patients with conflict-related injuries from the Russian-Ukrainian war. These patients are transferred from intermediate hospital centres, where they can remain for months and where there is great antibiotic pressure. Antibiotic resistance is currently a global problem, with inappropriate prescription of antibiotics in healthcare systems being one of the main causes.^{9,10} This means that one of the greatest challenges in their care is the high incidence of wound infection, as well as the presence of multi-resistant pathogens.

Our aim in this study was to characterise the microbial patterns of wounds caused by weapons of war in patients from the Russian-Ukrainian war transferred for treatment to the Zaragoza General Hospital of the Defence. We also sought to identify the patterns of antimicrobial resistance in the pathogens involved and define the factors associated with infection of wounds of this nature in these patients.

Methods

We included patients with war-related injuries from the Russian-Ukrainian conflict transferred from Ukraine and Poland and treated at the Zaragoza General Hospital of the Defence from

May 2022 to October 2023. Patients who were referred exclusively for rehabilitative treatment and who did not have open wounds or require surgical treatment were excluded.

This study was carried out with the approval of the Independent Ethics Committee for Research with Medicines at the Hospital Central de la Defensa Gómez Ulla (HCDGU IECm), code 27/23.

Data collection

The information recorded for each patient included basic epidemiological data (age and gender), the injury mechanism, its anatomical location, the presence of bone injury, skin loss and/or foreign bodies, and the time from the injury to transfer to our centre.

We collected the microbiological results of all cultures taken from the patients from combat-related or surgical wounds. We recorded the number of cultures, the origin, the type of sample and the microorganisms isolated, as well as their corresponding antibiotic sensitivity pattern and resistance profile.

To define cases of infection, we used occurrence of any of the following criteria: appearance of purulent discharge; signs of local inflammation; or undue delay in scarring. The presence of analytical signs of infection supported the diagnosis, but was not a necessary criterion. Colonisation was defined by positive growth on the swab taken for epidemiology on admission of the patient, or by wound cultures with no data of active infection (such as those mentioned above).

As per protocol, patients referred for inpatient treatment had swabs taken for epidemiology on arrival, while those treated as outpatients did not have them routinely performed on arrival.

Culture and identification

The samples were processed and plated on conventional culture media (blood agar, chocolate agar, MacConkey agar, Schaedler agar and liquid trypticase-soy enrichment medium). The microorganisms isolated were identified by MALDI-TOF mass spectrometry (Bruker Daltonics).

Antibiotic sensitivity and resistance mechanisms

Antibiotic sensitivity was performed using the automated Microscan WalkAway method (Beckman Coulter), disc plate (Oxoid) and/or gradient strip (Liofilchem), applying the EUCAST criteria in force for the interpretation of results.

The detection of CTX-M extended-spectrum beta-lactamase (ESBL) and KPC, OXA-48-like, NDM, IMP and VIM carbapenemases was performed by lateral flow immunochromatography (NG-test CTX-M, NG-test CARBA, NG-Biotech).

Table 1

Summary of the data obtained from the patients included in the study.

Variable	Number of patients	% (n = 53)
<i>Anatomical location</i>		
Upper limb	27	50.9%
Lower limb	19	35.8%
Torso	5	9.4%
Head	3	5.6%
<i>Injury mechanism</i>		
Explosion	44	83%
Bullet	7	13.2%
Fall	2	3.7%
<i>Wound culture</i>		
Positive	17	32%
Negative ^a	36	67.9%
<i>Number of microorganisms</i>		(n = 17)
1	9	52.9%
2	4	23.5%
> 2	4	23.5%

^a No culture taken, or it was negative.

Statistical analysis

We analysed the correlation between the presence of infection and the presence of soft tissue injury, bone injury and foreign bodies (shrapnel) and the time until transfer. We also analysed the correlation between time until transfer and the presence of bacterial infection.

The data obtained were analysed using SPSS software version 19-0 (IBM Corporation). For the comparison of groups, we used the T-test for independent samples, considering a $p < 0.05$ as statistically significant.

Results

In the period from May 2022 to October 2023 we treated a total of 71 patients from different areas of Ukraine whose injuries were classified as war wounds according to internationally recognised criteria.¹¹ Eighteen of the 71 patients were excluded from the study because they were being seen for exclusively rehabilitative treatment; they did not have active injuries and nor had they received surgical care at our centre.

Of the 53 patients included in the study, 52 were male and one female. The average age of the patients in the series was 35.58. As regards injury mechanisms, 44 were wounds caused by explosives (83%); seven patients had bullet wounds (13.2%) and two patients had injuries caused by a fall (3.7%).

By location, 27 had injuries in the upper limbs, 19 in the lower limbs, five in the torso and three had head wounds (four had injuries in various locations).

All patients reported having received empirical antibiotic therapy after the injury. However, it was not possible to establish the antibiotic treatment prior to the transfer of the patients or its correlation with the development of antibiotic resistance, as data on the drugs used or the duration of treatment were not received systematically.

Positive cultures were obtained from the wounds of 17 patients (30%) from tissue or bone biopsies (Table 1). In the remaining 36, no clinical infection was observed, nor were isolates obtained in wound cultures. In the 17 patients with wound infection, a mean of 4.47 cultures were taken per patient.

Patients with wound infection had a mean age of 37.71, while patients without infection had a mean age of 34.58. No statistical difference was found between the two groups.

In terms of time from the initial injury to transfer to our centre, in patients with a diagnosed infection, the mean time until transfer was 113 days, while in patients without infection, the mean was

Table 2

Microorganisms isolated in the patients included in the study.

Microorganism	N.º of patients	Percentage of infected patients (n = 17)
<i>Klebsiella pneumoniae</i>	8	47%
<i>Staphylococcus aureus</i>	6	35.3%
<i>Pseudomonas aeruginosa</i>	4	23.5%
<i>Staphylococcus epidermidis</i>	3	17.6%
<i>Enterobacter cloacae</i>	2	11.7%
<i>Providencia stuartii</i>	2	11.7%
<i>Acinetobacter baumannii</i>	2	11.7%
<i>Proteus mirabilis</i>	1	5.8%
<i>Enterococcus faecalis</i>	1	5.8%
<i>Finnegoldia magna</i>	1	5.8%
<i>Escherichia coli</i>	1	5.8%
<i>Morganella morganii</i>	1	5.8%

93.72 days. No statistical difference was found between the two groups.

Bone injuries were more common in patients with infection (94.1% [16 of 17 patients] vs 66.6% [24 of 36 patients] [$p = 0.030$]), as was the presence of skin loss (58.8% [10 patients] vs 5.5% [two patients]) [$p = 0.000$].

As regards the identification of foreign bodies (shrapnel) in the X-ray, 13 of the 17 patients with infection had shrapnel in the wound bed (76.47%), compared to 13 of the 36 patients without infection (36.11%). A statistically significant difference was found ($p = 0.006$).

Microorganisms isolated and susceptibility patterns

Of the 17 patients with positive bacterial cultures, nine (52.9%) had a single microorganism isolated, four (23.5%) had two microorganisms and the remaining four (23.5%), polymicrobial cultures with three or more isolates (Table 1).

The microorganisms most frequently found in the wounds were Gram-negative bacilli, with *Klebsiella pneumoniae* in eight patients and *Pseudomonas aeruginosa* in four patients. Of the Gram-positive cocci, *Staphylococcus aureus* was isolated in six patients. The isolated microorganisms are shown in Table 2.

Among the Gram-negative microorganisms, all showed some resistance mechanism or several combined mechanisms (ESBL, carbapenemases, or being extremely drug resistant [XDR]), with the exception of one isolate of *Proteus mirabilis* and one isolate of *P. aeruginosa*, which were not XDR, and nor were ESBL or carbapenemases detected (Table 3). The most frequent carbapenemase detected in Enterobacteriaceae was NDM (in four isolates), followed by KPC and OXA-48 in three isolates, respectively. In *P. aeruginosa* the carbapenemases detected were VIM, IMP and GES in one isolate respectively. ESBL and double-carbapenemase OXA-48 and NDM were detected in one isolate of *K. pneumoniae*.

It should be noted that *Providencia stuartii* carrying NDM carbapenemase was detected in two patients, only being sensitive to aztreonam and cefiderocol.

The antibiotic sensitivity patterns of the main Gram-negative isolates are shown in Table 4.

Discussion

In our study we have described war weapon-related infections in patients treated in the Russian-Ukrainian war transferred to the Zaragoza General Hospital of the Defence in Spain, and determined the causative microorganisms, antibiotic sensitivity patterns and resistance mechanisms. Our work shows a correlation between the presence of shrapnel, bone lesions, skin loss, and infections caused

Table 3

Types of sample, location and microorganisms isolated in the 17 patients with positive cultures.

Patient	Date	Sample type	Gram-positive isolates	Gram-negative isolates and resistance mechanism
1	20/06/2022	Surg. wound	<i>S. epidermidis</i>	
2	01/07/2022	Surg. wound	MRSA	
3	21/07/2022	Surg. wound		<i>K. pneumoniae</i> OXA-48
4	30/08/2022	Biopsy	<i>S. epidermidis</i>	
5	07/09/2022	Surg. wound	<i>E. faecalis</i>	<i>A. baumannii</i> XDR
6	07/11/2022	Surg. wound		<i>K. pneumoniae</i> ESBL
7	09/12/2022	Surg. wound		<i>E. cloacae</i> ESBL
7	02/02/2023	Biopsy	MSSA	<i>A. baumannii</i> XDR
8	03/01/2023	Surg. wound		<i>E. cloacae</i>
8	03/02/2023	Biopsy		<i>P. stuartii</i> NDM
9	03/02/2023	Biopsy		<i>K. pneumoniae</i> ESBL + OXA-48 + NDM
10	27/02/2023	Surg. wound		<i>P. aeruginosa</i> XDR IMP
10	07/03/2023	Surg. wound	MSSA	<i>P. aeruginosa</i> XDR
10	18/08/2023	Surg. wound	<i>S. epidermidis</i>	<i>E. cloacae</i> ESBL
11	17/03/2023	Surg. wound	<i>Fingoldia magna</i>	<i>P. aeruginosa</i>
12	17/04/2023	Surg. wound	MRSA	<i>K. pneumoniae</i> KPC
13	25/05/2023	Ulcer		<i>P. aeruginosa</i> XDR
14	30/05/2023	Surg. wound		<i>P. aeruginosa</i> XDR VIM
15	13/06/2023	Surg. wound		<i>P. mirabilis</i>
16	28/07/2023	Surg. wound		<i>P. stuartii</i> NDM
17	08/08/2023	Surg. wound	MSSA	<i>M. morgani</i> ESBL
				<i>P. aeruginosa</i> XDR, GES
				<i>K. pneumoniae</i> ESBL, OXA-48
				<i>E. coli</i> ESBL
				<i>K. pneumoniae</i> ESBL, NDM
				<i>K. pneumoniae</i> KPC

ESBL: extended spectrum beta-lactamase; Surg.: surgical; MRSA: Methicillin-resistant *S. aureus*; MSSA: Methicillin-susceptible *S. aureus*; XDR: extensively drug resistant.**Table 4**

Antibiotic sensitivity patterns of the main Gram-negative bacilli isolated in the study.

	<i>Klebsiella pneumoniae</i> (n = 8) % S	<i>Pseudomonas aeruginosa</i> (n = 4) % S	<i>Acinetobacter baumannii</i> (n = 2) % S
Cefotaxime	12.5	–	–
Ceftazidime	12.5	16.6	–
Cefepime	12.5	16.6	–
Aztreonam	12.5	85	–
Piperacillin/tazobactam	12.5	16.6	–
Imipenem	12.5	16.6	–
Meropenem	12.5	16.6	–
Ertapenem	12.5	–	–
Ceftolozane-tazobactam	25	57	–
Ceftazidime-avibactam	75	57	–
Cefiderocol ^a	80	100	100
Amikacin	25	16.6	0
Gentamicin	37.5	–	0
Tobramycin	25	16.6	0
Ciprofloxacin	0	16.6	0
Trimethoprim-Sulfamethoxazole	25	–	0
Colistin	100	100	100
Fosfomycin (IV)	62.5	100 ^c	–
Tigecycline ^b	37.5	–	100

^a Cefiderocol tested on five isolates of *K. pneumoniae*, three isolates of *P. aeruginosa* and two isolates of *A. baumannii*.^b EUCAST PK/PD breakpoints.^c 100% of isolates with MIC < 32 mg/l (ECOFF < 256 mg/l).

by weapons of war. The majority of infected patients had mono-microbial cultures for Gram-negative microorganisms.

As far back as during the Vietnam War Heggers et al.¹² conducted a study that included 100 war wounded with limbs requiring amputation. In these patients, 92% of the infections were due to a single bacterium, the most common microorganisms being *P. aeruginosa*, *S. aureus*, *P. mirabilis* and *K. pneumoniae*. In our series, nine of the 17 infections were mono-microbial (52.9%). If we focus on more recent wars, and more specifically those occurring in

the Middle East, a lower incidence is to be found of *Acinetobacter baumannii*.^{13,14} Despite this, when comparing our series with recently published data from Ukrainian patients involved in the war,^{5,6,15} similarities are seen in the microorganisms found.

These microorganisms could have been acquired on the battlefield, but the high degree of multidrug resistance found suggests a nosocomial acquisition in the patients' hospitals of origin (Ukraine and Poland). High rates of multidrug resistance have been described both in Ukrainian military patients⁵ and in hospitals in Ukraine

and neighbouring countries.^{16,17} The microorganisms isolated and the resistances detected coincide with what is described in the literature for patients from Ukraine,^{5,6,17} with the exception of *A. baumannii*, which was rare, and was only isolated in two patients. Despite the origin being outside our centre, it is not uncommon for war-wounded patients to be unaware of the presence of infection until they have been treated by us, which can and does give rise to accusations of iatrogenicity.¹⁸

Although it would be interesting to study the correlation between colonisation on arrival and development of infection, this issue goes beyond the scope of this study. We should also point out that, despite the high prevalence of infection by multi-resistant germs, it is difficult to establish recommendations aimed at their prevention, since the initial antibiotic treatments are administered in a war zone, where interrupted access to microbiology analysis or the supply of antibiotics and over-saturation of the Ukrainian healthcare system make it difficult to provide targeted treatments. However, in cross-border destination countries, the development of infection should raise suspicion of the involvement of multidrug-resistant germs and trigger implementation of multidisciplinary management that involves team members from Programs for Optimizing the use of Antibiotics (PROA), and of preventive measures to avoid the spread of these pathogens in the hospital setting.

In terms of injury mechanisms, the last century has seen an increase in the proportion of war wounds caused by explosives compared to gunshot wounds. Wounds due to explosives represented 35% of injuries during the First World War,¹⁹ 65% during the Vietnam War²⁰ and 74.4% during the recent conflicts in Afghanistan and Iraq.²¹ In our case, the proportion of injury due to explosives reached 83% of all injuries, confirming the increasing trend of such devices. This trend corresponds to the simplicity of manufacturing, use and effectiveness of explosive devices in a combat environment compared to guns.²¹

As we pointed out earlier, it is apparent that the changes in the injury mechanism have not meant a change in the pathogens.¹² This corresponds to the origin of the pathogens being from the environment where the injuries occur and not from the injury-causing material itself. However, it should be noted that, although the pathogens are similar, injuries caused by explosives usually affect a much larger surface area and result in a greater amount of foreign bodies and devitalised tissue, so their clinical and surgical treatment is more complex.²²

Our work shows a statistically significant correlation between the presence of war-wound infection and the three factors typical of wounds caused by explosive devices (the presence of soft tissue defect, bone injury and shrapnel).^{11,22} This suggests the greater infectious potential of wounds produced in this way. Given the few cases of gunshot injuries observed in this conflict, it is difficult to make a direct analysis of the incidence of infections between the two causes. In our hospital practice, this correlation between the three factors inherent to shrapnel injuries has led us to manage the patients in whom they converged as patients with active infection awaiting culture.^{11,23,24}

Focusing on the infected patients, as has previously been described in this type of patient, the systematic presence of antibiotic resistance found is entirely to be expected.^{5,6,17} It should be noted that military medical care is divided into four Roles, with the Zaragoza General Hospital of the Defence in Spain acting as Role 4, that is, definitive patient care in with the country. This division implies that all war-wounded patients have previously received antibiotic treatment, especially in field hospitals. For obvious logistical issues, it is no surprise that in the earlier stages there is no access to adequate antibiotic treatment for these injuries. Added to this is the fact that, in this particular conflict, the Ukrainian healthcare network has lost much of its structure. This is why, for the definitive care of many of its injured, it is relying on third coun-

tries, where in many cases there is a very high consumption and turnover of antibiotics, as well as high rates of resistance.^{16,17} This dependency means that the transfer to Role 4 can be delayed for lengthy periods, which is why the pathogens we have found in our series are multidrug-resistant. The problem with antibiotic resistance associated with war wounds has been widely reported.^{7,25,26} Therefore, in terms of the management of these patients, it is of particular interest to have early transfer to the centres where they will receive their definitive treatment.

We should stress that we have not undertaken any in-depth study of the resistances we found as this was not the subject of this article, nor have we described the treatments or results, which due to their complexity and peculiarities would merit a separate study. We can say, however, that despite the complexity of management to be expected from these infections, only two patients have required amputation so far and no deaths have been recorded.

Lastly, we must emphasise once more the importance of controlling infection by these multi-resistant microorganisms in the healthcare environment, a challenge, given the fact that these patients have been treated by various specialities with sometimes very long stays in hospital. Nevertheless, no isolates of these pathogens have been detected in other users of the healthcare centres involved.

In conclusion, our work confirms the trend observed during the 20th century in greater use of explosives in warfare, and a correlation between the characteristics of these injuries and the presence of infection. The collapse of healthcare systems and inadequate antibiotic treatment in countries at war continues to lead to a very high incidence of multidrug-resistant bacteria, similar to previous war conflicts. Despite the passage of time, war is still war.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

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