Meeting of the FEAMC Executive Board with a Conference on Professional and Ethical Challenges in Medicine During Wartime

Đakovo – Vukovar, Croatia

The impact of armed conflict on the development and global spread of antibiotic resistance

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- **Armed conflicts have been implicated in antimicrobial resistance development.**

- **Cases of antimicrobial-resistant microorganisms in people with war injuries were first documented during World War II and have been increasingly reported during more recent conflicts.**

Rustigan R et al. JAMA 1947;133:224-9.
Lindberg RB et al. Ann Surg 1955;141:369-74.
Altemeier WA. JAMA 1944;124:413e7.
DeWaal HL. Edinburgh Med 1943;50:577-88.
Mende K et al. Mil Med 2022;187:42-51.

- **Currently, the high rate of carbapenemase-producing P. aeruginosa, Acinetobacter baumannii and K. pneumoniae from war wounds in Ukraine is of particular concern.**

- **The conflict in Ukraine has led to the displacement of people from Ukraine and the transfer of thousands of patients from Ukrainian hospitals to medical facilities in various countries.**

Salmanov A et al. J Hosp Infect 2023;131:129-38.
Higgins PG et al. Antibiotics (Basel) 2020; 9: 579.
Melwani M. BMJ 2022;379:o2731.
European Commission (EC). https://civilprotection-humanitarian-aid.ec.europa.eu/news-stories/news/ukraine-2000-ukrainian-patients-transferred-european-hospitals-start-war-2023-03-23_en
The UN Refugee Agency (UNHCR). unhcr.org/en/situations/ukraine.

The burden of antibiotic resistance during armed conflicts

High rates of MDR *A. baumannii*, extended-spectrum b-lactamase (ESBL)-producing *Klebsiella pneumoniae*, and Methicillin-resistant *Staphylococcus aureus* (MRSA) in Iraq and Afghanistan

- ✓ A large retrospective study evaluated the incidence of MDR *A. baumannii* and P. aeruginosa isolates in a military hospital during the Iraqi conflict.
- ✓ The study period lasted for 8 years, during which 124 205 local civilian and military patients and 3333 combat casualties were admitted.
- ✓ The percentage of MDR *A. baumannii* isolates increased from 4% to 55% ($p < 0.009$)

M'Aiber S et al. J Glob Antimicrob Resist 2022;30:311-8

High rates of MDR *A. baumannii*, extended-spectrum b-lactamase (ESBL)-producing *Klebsiella pneumoniae*, and Methicillin-resistant *Staphylococcus aureus* (MRSA) in Iraq and Afghanistan

- In a surveillance study of combat-injured personnel from Afghanistan and Iraq admitted to four military hospitals in the US and Germany, 6% (171 out of 2989) of patients were colonized at admission.

- Of these, 29% were colonized with A. baumannii, 57% with ESBL-producing Escherichia coli, and 11% with ESBL-producing Klebsiella spp

Hospenthal DR et al. J Trauma 2011;71:S52-7.

High rates of MDR *A. baumannii*, extended-spectrum b-lactamase (ESBL)-producing *Klebsiella pneumoniae*, and Methicillin-resistant *Staphylococcus aureus* (MRSA) in Iraq and Afghanistan

- ✓ In relation to infections caused by *A. baumannii*, a study was conducted on soldiers who were admitted with osteomyelitis or wound infection during the Iraqi conflict.
- ✓ Before the onset of the military operations *Acinetobacter* spp. accounted for only the 0.6% of the isolates.
- ✓ In contrast, after the start of the conflict, 151 active-duty soldiers were admitted for combat injury, and 30 (19%) had clinical infection due to *Acinetobacter* spp. ($p < 0.01$).

Davis KA et al. Emerg Infect Dis 2005; 11:1218-24

High rates of MDR *A. baumannii*, extended-spectrum b-lactamase (ESBL)-producing *Klebsiella pneumoniae*, and Methicillin-resistant *Staphylococcus aureus* (MRSA) in Iraq and Afghanistan

- ✓ A study by Hujer et al. characterised resistance genes from 75 isolates of Acinetobacter spp. obtained from severely ill military and civilian patients from the Iraq and Afghanistan conflict.
- ✓ The study found that meropenem resistance was detected in 25% of the isolates.
- ✓ Out of the five classes of antibiotics tested, 11 isolates (15%) were resistant to all of them.
- ✓ The resistance genes “ADC” and “OXA-69-like” were present in all of the strains, and the “OXA-58-like” gene was also detected

Davis KA et al. Emerg Infect Dis 2005; 11:1218-24

First reports of New Delhi metallo-b-lactamase producing enterobacteria from the Libyan and the Syrian conflicts

- ✓ A surveillance study observed that 60% of 67 patients transferred to Germany after being injured during the Libyan war were colonized or infected with MDR organisms.
- ✓ Of these, 37.3% were positive for carbapenem-resistant organisms and 16.4% had MRSA.
- ✓ Out of the 37 isolates of K. pneumoniae, A. baumannii, E. coli, E. cloacae, and S. marcescens, carbapenemases such as New Delhi metallo-b-lactamase (45%), OXA-48 (40%) and OXA-23 (24%) were identified, along with other b-lactamases (mostly CTX-M-group-1) and plasmid-mediated quinolone resistance genes.

Lohr B et al. Microb Drug Resist 2018;24:578-84.

High rates of New Delhi metallo-b-lactamase and OXA-48 producing Enterobacterales during the Ukraine conflict

- ✓ Recently, a study reported on 141 patients who required emergency surgery for burns, shrapnel wounds and fractures during the war in Ukraine.
- ✓ Out of 154 isolates, 89 (58%) were resistant to meropenem.
- ✓ In addition, 49% of the tested strains were resistant to cefiderocol and high rates of resistance to ceftazidimeeavibacta (80%), ceftolozane-tazobactam (95%), imipenem-relebactam (84%) and meropenem-vaborbactam (80%) were reported. Finally, 9 (6%) isolates, all K. pneumoniae, were resistant to all antimicrobials tested.
- ✓ Screening for carbapenemase genes revealed a dominance of New Delhi metallo-b-lactamase and OXA-48

Ljungquist O et al. Lancet Infect Dis 2023;23:784-6

High rates of New Delhi metallo-b-lactamase and OXA-48 producing Enterobacterales during the Ukraine conflict

- ✓ A study evaluated MDR Gram-negative bacteria in refugees and war-wounded Ukrainians using whole-genome sequencing.

- ✓ The most commonly detected carbapenemases were New Delhi metallo-b-lactamase (reported in 17 of 25 isolates) and OXA-48 (6 of 25 isolates).

- ✓ Berger et al. described infections caused by carbapenemase-producing Gram-negative bacteria in five Ukrainian war-disabled patients, all of whom had infections due to New Delhi metallo-b-lactamase-1-producing K. pneumoniae.

Stein C et al. Infection 2023;51:1731-8
Berger FK et al. Int J Infect Dis 2023;132:89-92

High rates of New Delhi metallo-b-lactamase and OXA-48 producing Enterobacterales during the Ukraine conflict

- ✓ the Netherlands: analysis of the epidemiology and genetic profile of MDR pathogens among Ukrainian patients. 60% of the 62 Gram-negative isolates carried New Delhi metallo-b-lactamase carbapenemases.

- ✓ A retrospective microbiological survey conducted in Germany on over 17 000 isolates documented an increase in New Delhi metallo-b-lactamase-1 and OXA-48 producing K. pneumoniae among refugees and soldiers from Ukraine.

- ✓ In a multi-centre microbiological survey conducted in Ukrainian military hospitals between 2014 and 2020 among 162 patients, more than 50% of the P. aeruginosa, E.coli, K. pneumoniae and A. baumannii isolates were resistant to four or five antimicrobial groups.

Zwittink RD et al. Euro Surveill 2022;27:2200896.
Sandfort M et al. Euro Surveill 2022;27: 2200926.
Kondratiuk V et al. J Hosp Infect 2021;112:69-76

Causes of antibiotic resistance increase during armed conflicts

Is soil the source of MDR isolates?

- ✓ **An active surveillance study was conducted to assess the presence of MDR Gram-negative organisms in soil samples from Afghanistan and Iraq, as well as in field hospitals.**

- ✓ **The absence of MDR isolates in soil samples and the limited aerosolization of these organisms during surgical procedures support that nosocomial transmission was the primary source rather than environmental contamination.**

Keen EF 3rd et al. Infect Control Hosp Epidemiol 2012;33:905-11.

Role of the healthcare setting

- ✓ **In 2014, a surveillance study was conducted at the military hospital of Vinnytsia, Ukraine, to investigate the bacterial microbiota of extremity wounds in 49 military patients with combat related injuries.**
- ✓ **The study found that over time, there was an increase in the occurrence of polymicrobial wound cultures.**
- ✓ **The shift in wound microbiology towards bacteria associated with healthcare-associated infections could be attributed to nosocomial transmission.**

Valentine KP et al. BMC Res Notes 2017;10:152.

- ✓ **A surveillance study investigated the sources of an outbreak of MDR A. baumannii infections among U.S. soldiers evacuated from Iraq.**
- ✓ **On average, patients received treatment at more than three facilities before being admitted to the study hospital.**
- ✓ **On average, patients arrived at one of these facilities within 5.7 days of their injury.**
- ✓ **Based on the antimicrobial susceptibility profile, the authors concluded that the outbreak was primarily caused by nosocomial transmission in the field hospitals in Iraq.**

Scott P et al. Clin Infect Dis 2007;44:1577-84.

Inappropriate use of antibiotics and other risk factors for antimicrobial resistance development during conflicts

- ✓ **A prospective observational study was conducted to examine the risk factors for MDR Gram-negative bacteria colonization among injured military personnel evacuated from the Iraqi conflict.**

The identified risk factors included

- **sustaining an injury during the high combat season (odds ratio: 1.76; 95% CI: 1.31-2.35),**
- **requiring blood transfusion within 24 hours of injury (odds ratio: 2.80; 95% CI: 1.63-4.81),**
- **and receiving cefazolin (with or without other antibiotics) (odds ratio: 3.50; 95% CI: 1.54-7.93)**

Gilbert LJ et al. Diagn Microbiol Infect Dis 2016;84:358-60.

Take Home Messages

- ✓ **Combat-related injuries among soldiers often result in devitalized and contaminated tissue, favouring the development of antimicrobial resistance.**

- ✓ **Also, incomplete disinfection procedures and environmental transmission are probably significant factors in the spread of MDR bacteria in military medical facilities.**

- ✓ **These challenges are particularly pronounced in mass casualty situations, where practices such as cohorting, isolation, and proper handwashing are difficult to implement.**

Granata G et al. Clin Microbiol Infect 2024:S1198-743X(24)00160-5.

- ✓ **The disruption of the healthcare system and people gathering in shelters for protection may contribute to the spread of MDR pathogens from soldiers to civilians in war zones.**

- ✓ **Training healthcare providers in military hospitals and soldiers about the proper use of antibiotics is a crucial initiative to reduce antibiotic resistance during wartime operations.**

- ✓ **It is important to implement rigorous infection control measures, such as frequent cleaning and disinfection of hospital and battlefield facilities, as well as measures to prevent the transmission of bacteria from infected patients to others, for instance, by screening at admission and implementing cohort isolation.**

Petrosillo N et al. Lancet Infect Dis 2023;23(6):653-654.