



Short Communication

Coexistence of seven different carbapenemase producers in a single hospital admission screening confirmed by whole-genome sequencing



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ABSTRACT

Objective: To molecularly characterize several extensively drug-resistant isolates from a single hospital admission screening of a war-injured patient from Ukraine.

Methods: Admission screening included swabs from skin, wounds, catheters, nasopharynx and rectum. Bacterial identification, antimicrobial susceptibility testing and rapid multiplex PCR assays targeting resistance genes were performed during routine diagnostics. Isolates positive by PCR had their genomes sequenced using short- and long read-platforms (MiSeq and MinION) to confirm species, identify resistance genes and plasmids and investigate clonality with core-genome MLST.

Results: Seven Gram-negative pathogens (*Acinetobacter baumannii* (n = 2; ST78, ST2), *Klebsiella pneumoniae* (n = 2; ST395), *Pseudomonas aeruginosa* (n = 1; ST1047), *Escherichia coli* (n = 1; ST46), *Enterobacter cloacae* complex (n = 1; ST231)) were molecularly confirmed non-identical. Antimicrobial susceptibility testing showed resistance to carbapenems (7/7 isolates) and last-resort treatment options such as ceftazidime-avibactam (6/7 isolates) and cefiderocol (4/7 isolates). All isolates were colistin susceptible. Sequencing identified the *E. cloacae* complex as *Enterobacter hormaechei* subsp. *xiangfangensis*. Six acquired carbapenemase genes (*bla_{IMP-1}*, *bla_{NDM-1}*, *bla_{OXA-48}*, *bla_{NDM-5}*, *bla_{OXA-23}* and *bla_{OXA-72}*) were detected. Both *A. baumannii* isolates differed in sequence type, carbapenemases and cefiderocol susceptibility. Both *K. pneumoniae* isolates shared sequence type and some resistance genes on an IncR plasmid but were different in core-genome MLST and carbapenemases (OXA-48 or NDM-1). One vancomycin-resistant *Enterococcus faecium* was also detected (*VanA*).

Conclusions: War-injured patients from Ukraine may carry different clones of multidrug-resistant pathogens with limited treatment options and diverse resistance genes at risk for dissemination. Infection control measures should include early molecular characterization of isolates for detection of routes of transmission.

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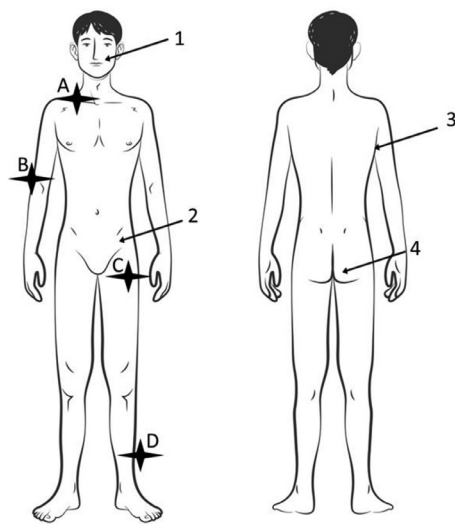
1. Introduction

Among the millions of Ukrainian refugees that were displaced since 2022, some with medical needs were admitted to hospitals across Europe [1]. Routine hospital admission screenings for patients at risk for carriage of multidrug-resistant (MDR) pathogens

may guide infection control measures to prevent intra-hospital dissemination of isolates or mobile genetic elements harbouring resistance genes [2,3]. The prevalence of MDR-pathogens among patients from Ukraine is considered high and screening results may also guide antimicrobial therapy if needed [2,4,5]. In this study, non-identical extensively drug-resistant (XDR) isolates from a single hospital admission screening of one war-injured Ukrainian male were molecularly characterized. The refugee was evacuated from a Ukrainian hospital to the Military Central Hospital in Koblenz, Germany, with a shrapnel injury from a battlefield explo-

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Fig. 1. Isolates displayed by site of isolation; Arrows 1, 2, 3 and 4 indicate regular hygiene screening sites (nasopharynx, groin, armpit, rectum) and compass rose A, B, C and D indicate additional sites of screening: A: Central venous catheter (CVC)-Tip, B: right elbow wound, C and D: left upper leg and left lower leg deep tissue wounds, respectively. Some isolates (*Acinetobacter baumannii* blaOXA-72 and *Klebsiella pneumoniae* blaNDM-1) were found in regular screening and in additional screening sites. Some isolates were only found in one site (e.g. *Pseudomonas aeruginosa* blaIMP-1 only found on CVC-Tip and *A. baumannii* blaOXA-23 only found in deep upper leg wound) or only in regular hygiene screening and not in wounds (*K. pneumoniae* blaOXA-48); Interestingly, the *A. baumannii* blaOXA-72 was present in all screening sites but the rectal swab.

Isolation Site	Isolates	Comment
Regular Hygiene Screening	1 <i>A. baumannii</i> bla _{OXA-72} <i>K. pneumoniae</i> bla _{NDM-1} <i>E. coli</i> bla _{NDM-5} <i>E. hormaechei</i> subsp. <i>xiangfangensis</i> bla _{NDM-1}	4 out of 8 isolates, All NDM-plasmids of the patient in one site, but different in WGS Only site with <i>E. hormaechei</i> subsp. <i>xiangfangensis</i>
	2 <i>A. baumannii</i> bla _{OXA-72} <i>K. pneumoniae</i> bla _{OXA-48} <i>E. coli</i> bla _{NDM-5}	3 out of 8 isolates
	3 -	0 out of 8 isolates
	4 <i>E. faecium</i> VRE <i>K. pneumoniae</i> bla _{OXA-48} <i>E. coli</i> bla _{NDM-5}	Only site with VRE, 3 out of 8 isolates
Additional sites	A <i>P. aeruginosa</i> bla _{IMP-1} <i>A. baumannii</i> bla _{OXA-72}	2 out of 8 isolates, only site with <i>P. aeruginosa</i> bla _{IMP-1}
	B <i>A. baumannii</i> bla _{OXA-72}	1 out of 8 isolates
	C <i>K. pneumoniae</i> bla _{NDM-1} <i>A. baumannii</i> bla _{OXA-23} <i>A. baumannii</i> bla _{OXA-72}	3 out of 8 isolates, only site with <i>A. baumannii</i> bla _{OXA-23}
	D <i>A. baumannii</i> bla _{OXA-72} <i>K. pneumoniae</i> bla _{NDM-1}	2 out of 8 isolates

sion about 3 weeks prior to admission in Germany. The molecular analysis of the screened isolates reported here highlights that carriage of multiple clones of different MDR pathogens may occur in the context of the war in Ukraine. Clinical risk assessments may guide infection prevention control policies in general terms, however, millions of war refugees are an extraordinary situation for which such general policies must still prove their ability to be reliable. The identification and molecular characterization of MDR isolates from Ukraine is therefore necessary to gain knowledge on the epidemiology and distribution of isolates in countries, like Germany, that still have a relatively low prevalence of XDR-isolates based on current surveillance data [6]. This applies to many countries in western Europe currently admitting conflict-associated patients, alongside reports of rising XDR-prevalence related to the conflict [6,7]. Detailed molecular data on such isolates paves the way to detect the routes of transmission and contributes to best possible infection prevention control, however, these data are still limited.

2. Methods

2.1. Bacterial isolates, culture conditions, antimicrobial susceptibility testing

Samples from admission included routine screening swabs from nasopharynx, armpit, rectum and groin (Fig. 1). In addition, the tip of a jugular CVC and multiple wound swabs (upper and lower left leg, elbow) were investigated. Samples were plated on selective culture media for MRSA (CHROMagar MRSA, Paris, France), *A. baumannii* (CHROMagar Acinetobacter, CHROMagar, France), vancomycin-resistant *Enterococcus faecium* (VRE) (VRE, Biomérieux, Nürtingen, Germany), extended-spectrum beta-lactamases (ESBL Brilliance, Oxoid, Wesel, Germany) and enrichment broth (Thioglycollate Becton Dickinson, Maryland, USA). For antimicrobial susceptibility testing (AST) the VITEK2 system (AST N429 and N429 cards; BioMérieux, Germany) was used. Additional testing of ceftazidime/avibactam, ceftolozane/tazobactam

(agar gradient strips, Oxoid, Germany), colistin (broth microdilution, Merlin Diagnostika, Bornheim, Germany), tigecycline (broth microdilution, Merlin Diagnostika, Germany) and cefiderocol (broth microdilution using ComASP plates and cation-adjusted iron-depleted Mueller-Hinton broth, Liofilchem, Roseto degli Abruzzi, Italy; and in-house plates, when repetition was necessary) was performed according to EUCAST recommendations and interpreted based on EUCAST breakpoints (version 12.0). During clinical routine testing, rapid detection of carbapenemases and vancomycin resistance was performed immediately with rapid PCR assays (GeneXpert, Carba-R kit and VanA/B, Cepheid, Frankfurt, Germany) and lateral flow assays (RESIST-3 O.O.K. and RESIST-5 O.K.N.V.I., Coris BioConcept, Gembloux, Belgium).

2.2. Genomic analysis (whole-genome sequencing, core-genome MLST)

Isolates with carbapenem resistance or detection of resistance genes had their genomes sequenced with short- and long-read platforms (MiSeq [Illumina GmbH, Munich, Germany] and MinION [Oxford Nanopore Technologies, Oxford, United Kingdom]) to confirm species identification, analyse resistance genes, plasmid content and investigate clonality using core-genome MLST as previously described [8–10].

3. Results and discussion

From the one hospital admission screening, eight pathogens of six different species (*A. baumannii* (n = 2), *Klebsiella pneumoniae* (n = 2), *Pseudomonas aeruginosa* (n = 1), *Escherichia coli* (n = 1), *Enterobacter hormaechei* subsp. *xiangfangensis* (n = 1), *E. faecium*, VRE (n = 1)) were identified and forwarded for sequencing. Six different acquired carbapenemase genes (bla_{IMP-1} (n = 1), bla_{NDM-1} (n = 2), bla_{OXA-48} (n = 1), bla_{NDM-5} (n = 1), bla_{OXA-72} (n = 1), bla_{OXA-23} (n = 1)) were detected in carbapenem-resistant Gram-negative isolates. By core-genome MLST all isolates were epidemiologically distinct from each other. Both *A. baumannii* isolates (ST78

and ST2, respectively) differed in 2155 out of 2290 alleles. The two *K. pneumoniae* isolates were different by 126 out of 2358 alleles and in carbapenemase content (plasmid-encoded OXA-48 and NDM-1, respectively). However, both had the same sequence type (ST395) and shared acquired resistance genes (*bla*_{CTX-M-15}, *bla*_{OXA-1} and *catB3*) encoded on an IncR plasmid (sizes of 36 and 68 kb, respectively), potentially indicating horizontal gene transfer. From the rectal swab a VRE (*VanA*-operon, susceptible to tigecycline and linezolid, resistant to vancomycin and teicoplanin) was also identified. A more detailed summary of resistance genes derived from whole-genome sequencing can be found in Supplementary Table S1. Table S1 also displays two additional MDR Enterobacterales isolates (*Proteus mirabilis* and *E. hormaechei* subsp. *hoffmannii*) from the same patient that were isolated a few days after hospital admission from surveillance cultures. Both were carbapenem-susceptible and also showed independent resistance gene content compared to the other isolates of the patient. Overall, sequencing indicated an independent epidemiological background and a distinct acquisition of resistance genes for all eight isolates.

Some isolates were present only in battlefield wounds and some isolates were only found in routine screening of skin, nasopharynx or rectum (Fig. 1). The screening procedure of each swab in the microbiology department, included different types of solid selective media and liquid enrichment broth. In line with previous reports, the isolates were resistant to multiple antimicrobials, including last-resort drugs with high proportion of metallo-beta-lactamases (NDM, IMP) [7]. The AST results for all carbapenem-resistant Gram-negative isolates are displayed in Table 1.

3.1. Molecular epidemiology

Our study documents the presence of eight high-risk clones of different pathogens upon hospital admission. All carbapenemases were acquired independently by the respective isolates, and all isolates were epidemiologically distinct from each other. However, some of the isolates reported here were molecularly similar to isolates from other studies.

3.1.1. *A. baumannii* and *P. aeruginosa*

The acquisition of OXA-23 and OXA-72 in *A. baumannii* isolates is well characterized in global lineages of carbapenem-resistant *A. baumannii*, and has been described for Ukraine and other countries previously [4,11,12]. In line with previous observations, the finding of an ST78 *A. baumannii* isolate may indicate successful circulation of these clones particularly in Russia and Ukraine although this lineage has been isolated worldwide, which earned it the moniker International clone 6 [4,5,13]. Our ST78 isolate shared many resistance genes with a previously characterized conflict-associated isolate [5]. In contrast to this report we found two different *A. baumannii* isolates of which one was cefiderocol-resistant (MIC of 128 mg/L, ST2, OXA-23) most likely associated with PER-7, detected in the genome of the ST2, OXA-23 isolate [14], while the other one was cefiderocol susceptible (MIC of 0.5 mg/L, ST78, OXA-72). Our study included one *P. aeruginosa* IMP-1 isolate that was cefiderocol susceptible, but ceftolozane/tazobactam did not show any activity (MIC >256 mg/L), despite being previously considered to be active particularly against MDR *Pseudomonas* isolates. Previous studies have identified acquired IMP-carbapenemases to confer ceftolozane/tazobactam non-susceptibility in *P. aeruginosa* [15,16]. Interestingly, IMP-1 harbouring *P. aeruginosa* isolates of the same sequence type have previously been reported by other authors describing current patients from Ukraine [5,17]. However, these studies did not include long-read sequencing methods, therefore data regarding plasmid content and mobile genetic elements were missing.

Table 1
Carbapenem-resistant isolates displayed by species with corresponding phenotypic susceptibility and molecular characterization.

Species	Collection ID	Carbapenemase	Sequence type	MICs (mg/L) and EUCAST interpretation (S/I/R)									
				CAZ	FEP	MER	IPM	TZP	CAZ/AVI	CTT	CEF	CIP	SXT
<i>A. baumannii</i>	22-01-08	OXA-72	ST78	-	-	≥16	≥16	-	>256	>256	0.5	≥4	160
<i>A. baumannii</i>	22-01-04	OXA-23	ST2	-	-	≥16	≥16	-	>256	>256	S*	R	R
<i>K. pneumoniae</i>	M 24	NDM-1	ST395	-	-	≥16	≥16	-	>256	>256	128	≥4	≥320
<i>K. pneumoniae</i>	22-01-11	OXA-48	ST395	≥64	≥32	≥16	≥16	≥128	>256	>256	R*	R	R
<i>P. aeruginosa</i>	22-01-02	IMP-1	ST1047	≥64	≥32	≥16	≥16	≥128	>256	>256	4	≥4	≥320
<i>E. coli</i>	M 23	NDM-5	ST46	≥64	≥32	8	8	≥128	>256	>256	4	≥4	≥320
<i>E. hormaechei</i> subsp. <i>xiangfangensis</i>	M 22	NDM-1	ST231	≥64	≥32	≥16	8	≥128	>256	>256	64	≥4	≥320
				R	R	R	R	R	R	R	R	R	R

S/I/R: Susceptibility according to EUCAST (*PK-PD)-breakpoints version 13.1; CAZ: Ceftazidime; FEP: cefepime; MER: meropenem; IPM: imipenem; TZP: piperacillin/tazobactam; CAZ/AVI: ceftazidime/avibactam; CTT: ceftolozane/tazobactam; CEF: cefiderocol; CIP: ciprofloxacin; SXT: trimethoprim/sulfamethoxazole; TOB: tobramycin; AZT: aztreonam; TIG: tigecycline; COL: colistin.

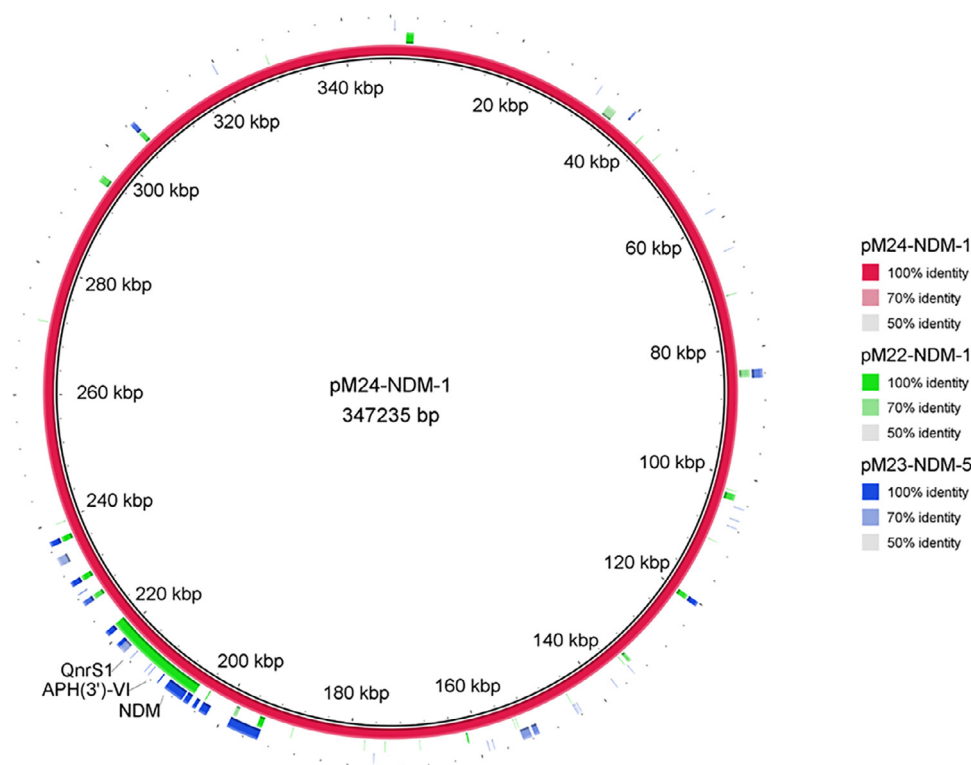


Fig. 2. Comparative plasmid analysis using BRIG of the NDM-encoding plasmids detected in *Klebsiella pneumoniae* (M24), *Enterobacter hormaechei* subsp. *xiangfangensis* (M22) and *Escherichia coli* (M23). The plasmids pM24-NDM-1 (red), pM23-NDM-5 (blue) and pM22-NDM-1 (green) differed in size, content and Inc type, indicating an independent acquisition of the carbapenemases and ruling out horizontal gene transfer.

3.1.2. Enterobacterales

Both *K. pneumoniae* isolates were ST395 but possessed different carbapenemases, NDM-1 or OXA-48, which are reported to be among the predominant variants in *K. pneumoniae* from Ukraine [7]. Interestingly, the NDM-1 isolate was ceftiderocol resistant, leaving only colistin as last-resort treatment option. The mechanism of ceftiderocol resistance is still an ongoing discussion, and resistance was also reported in other NDM-harboring isolates within our collection and previous observations [14,15,18]. Of the four Enterobacterales isolates, the three with an NDM-carbapenemase were all ceftiderocol resistant. The ST46 *E. coli* harbored an NDM-5 carbapenemase, which was reported as a predominant variant in another European cohort of patients previously hospitalized in Ukraine [19]. In our patient, the NDM-5 *E. coli* was the only isolate with a meropenem MIC in the EUCAST susceptible range (8 mg/L, susceptible, increased exposure), despite being MDR, which was also described in the cohort from the Netherlands [19]. The ST231/NDM-1 *E. hormaechei* subsp. *xiangfangensis* was also described in previous studies [19], however our results include a more detailed plasmid analysis of all NDM encoding plasmids (*E. hormaechei* subsp. *xiangfangensis* with NDM-1, *K. pneumoniae* with NDM-1 and *E. coli* with NDM-5) (Fig. 2). They differed in size, content and Inc type, indicating independent acquisition (Fig. 2). Interestingly, despite being epidemiologically unrelated, all three NDM-carrying pathogens were cultured from one swab (nasopharyngeum; Fig. 1).

3.2. Clinical presentation

With respect to clinical decision-making, which is not the focus of the present study, it is noteworthy that in contrast to previous reports [17], the patient did not receive accompanying antimicrobial therapy to the surgical treatment. However, the AST results from the screening revealed a combination of colistin (7/7 isolates

susceptible) and tigecycline (MIC range of 0.25 to 4 mg/L) as the most potent treatment for the patient, in case infectious complications would have been observed during patient stay. Of note, tigecycline breakpoints do not exist for all species reported here, however, the pharmacokinetic profile and the low tigecycline MICs documented here were considered beneficial in contrast to the limited other options for infectious wound complications. In brief, the patient suffered from extensive soft tissue wounds combined with injuries to arteries and nerves on the lower extremities and the right elbow. Overall, the patient was discharged after 17 weeks of hospital stay with several surgical interventions, including debridements for control of wound contamination and reconstructive tissue surgery. Tissue healing and functional result was considered good and re-evaluated by outpatient visits of the patient in the surgical department 2 and 42 weeks after discharge.

4. Conclusion

Our study documents the high rate of independently acquired resistance mechanisms of multiple different clones of XDR-pathogens, isolated upon hospital admission from a single patient with prior treatment in war-affected Ukraine. Admitting hospitals need to be aware of the necessity of careful screening policies, that should include early molecular characterization for detection of potential routes of transmission. Strategies to detect and characterize clones of pathogens are effective already at hospital admission. Established drugs, such as colistin and tigecycline may be more active in this cohort than novel cephalosporin-based antimicrobials, such as ceftiderocol or ceftolozane/tazobactam.

Author contributions

FF contributed to conceptualization, investigation, validation, writing the original draft, reviewing and editing. KX, TB, RAP, EW,

contributed to collection and characterization of isolates, reviewing and editing. FP and RMH contributed to investigation, collection of isolates, reviewing and editing. PH contributed to collection and characterization of isolates, writing and reviewing, conceptualization and validation. All authors approved the submitted version.

Sequence information

The raw sequencing reads generated in this project were submitted to the European Nucleotide Archive (<https://www.ebi.ac.uk/ena/>) under Bioproject accession number PRJEB75744.

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Declaration of competing interests: The authors declare no conflict of interest. RMH has received honoraria from Shionogi for consulting outside the presented work.

Ethical approval: The authors declare that the study was conducted in accordance with guidelines outlined by the Declaration of Helsinki. An informed consent was obtained from all subjects involved in the study.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at [doi:10.1016/j.jgar.2024.09.005](https://doi.org/10.1016/j.jgar.2024.09.005).

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