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Original Article

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First Isolates of OXA-48-Like Carbapenemase-Producing *Enterobacteriaceae* in A Specialized Cancer Center

Freddy Villanueva-Cotrina [1,2], **Dick Mamani Condori** [1], **Tamin Ortiz Gomez** [3,4], **Katia Mallma Yactayo** [1], **and Heli Barron-Pastor** [4]

[1]Department of Pathology, Instituto Nacional de Enfermedades Neoplasicas, Lima, Peru
[2]Department of Medical Microbiology, Universidad Nacional Mayor de San Marcos, Lima, Peru
[3]Department of Pathology, AUNA Laboratory. Lima, Peru
[4]Group of Research and Teaching in Molecular Medicine, Universidad Nacional Mayor de San Marcos, Lima, Peru

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Corresponding Author:
Freddy Villanueva-Cotrina, MD
Master in Science in Epidemiological Research, Instituto Nacional de Enfermedades Neoplasicas, Angamos Este avenue 2520, Surquillo 15038, Peru.
Tel: +511-94-208-3784
Email: freddyvillanue@gmail.com

ORCID iDs
Freddy Villanueva-Cotrina
https://orcid.org/0000-0001-8578-274X
Dick Mamani Condori
https://orcid.org/0000-0002-2615-7108
Tamin Ortiz Gomez
https://orcid.org/0000-0003-2857-5052
Katia Mallma Yactayo
https://orcid.org/0000-0002-4037-1637
Heli Barron-Pastor
https://orcid.org/0000-0002-4041-4406

ABSTRACT

Background: OXA-48-like carbapenemases have been found in a growing and varied number of carbapenemase-producing *Enterobacteriaceae* (CPE) isolates, and they are spreading to several countries. Although this oxacillinase leads to weak resistance to carbapenems without affecting broad-spectrum cephalosporin activity, when they are associated with other resistance mechanisms, the level of resistance to these antibiotics may be significantly higher. This weak resistance against carbapenems and cephalosporins, along with the absence of other resistance mechanisms, could render OXA-48-like harboring isolates undetected in the laboratory routine. In addition, the lack of a specific screening test for this enzyme complicates the detection of these isolates. This report characterizes the first isolates of OXA-48-like CPE detected in our laboratory.
Materials and Methods: The study was carried out at the Instituto Nacional de Enfermedades Neoplasicas, Lima - Peru, between March and December 2021. OXA-48-like CPE isolates were detected as part of the routine microbiological study, and clinical data were obtained by reviewing medical records. The automated microbiological system provides the bacterial identification and antimicrobial susceptibility profile by the dilution method. Additionally, the column chromatography test is used to detect carbapenemase enzymes, including OXA-48-like. Finally, the molecular identification of the OXA-48-like enzyme was carried out by Polymerase Chain Reaction PCR amplification for the $bla_{\text{OXA-48-like}}$.
Results: Seven OXA-48-like CPE strains were isolated. Notably, in all cases, the automated system issued a minimum inhibitory concentration (MIC) of ≥1 ug/mL for ertapenem and a MIC of >64/4 ug/mL for piperacillin/tazobactam. In addition, resistance category to imipenem and meropenem was found (2/7), at least one indeterminate category for any of these carbapenems (5/7), and other serine β-lactamases such as Extended-spectrum beta-lactamases (3/7) and AmpC (3/7). The immunochromatographic study confirmed the presence of the OXA-48-like enzyme in all isolates, while class A and class B were ruled out for them. Finally, the multiplex PCR, for the five isolates that could be recovered, showed amplification for carbapenemase OXA-48-like, while none of the other carpabemases was amplified for class A or class B carbapenemase genes.

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Conflict of Interest
No conflict of interest.

Author Contributions
Conceptualization: FVC, DMC, TOG. Data curation: FVC, DMC, TOG, KMY, HBP. Formal analysis: FVC, HBP, KMY. Investigation: FVC, DMC, TOG, KMY, HBP. Methodology: FVC, HBP, KMY. Writing - review & editing: FVC, DMC, TOG, KMY, HBP.

Conclusion: We confirm the emergence of OXA-48-like CPE isolates in our cancer center and highlight the need to implement surveillance and detection measures of these strains, for controlling their dissemination. We found practical and inexpensive methodologies for the detection of OXA-48-like CPE: (1) the finding of resistance to ertapenem and piperacillin/tazobactam in the antibiogram in the absence of class A and B carbapenemases, for screening and (2) immunochromatographic study, for confirmation.

Keywords: Emergence; Molecular identification; Oncology patients; Laboratory detection

INTRODUCTION

Carbapenemase-producing *Enterobacteriaceae* (CPE) infections cause high mortality [1, 2]. OXA-48-like carbapenemases have been found in a growing and varied number of CPE isolates, and they are spreading to several countries, thus becoming a threat to global public health [3, 4]. Although this oxacillinase leads to weak resistance to carbapenems without affecting broad-spectrum cephalosporin activity, when they are associated with permeability defects and Extended-spectrum beta-lactamases (ESBLs) production, the level of resistance to these antibiotics may be significantly higher [3]. This weak resistance against carbapenems and cephalosporins, along with the absence of other resistance mechanisms, could render OXA-48-like harboring isolates undetected in the laboratory routine. In addition, the lack of a specific screening test for this enzyme complicates the detection of these isolates. However, it was found that resistance to ertapenem and piperacillin/tazobactam in antimicrobial susceptibility testing may raise suspicion of OXA-48-like CPE [5, 6], while immunochromatographic and molecular techniques are necessary for confirmation [4]. This report characterizes the first isolates of OXA-48-like CPE detected in our laboratory.

MATERIAL AND METHODS

1. Strains, equipment and procedures

This study was carried out at the Instituto Nacional de Enfermedades Neoplasicas (INEN), Lima, Peru, between March and December 2021. OXA-48-like CPE isolates were detected as part of the routine microbiological study, and clinical data were obtained by reviewing medical records. Conventional and alternative methods are used routinely by the Microbiology Laboratory of INEN. The BD Phoenix automated microbiology system (Becton Dickinson, Diagnostic Systems, Sparks, MD, USA) provides the bacterial identification and antimicrobial susceptibility profile by the dilution method according to the guidelines of the Clinical and Laboratory Standards Institute (CLSI) 2020 [7]. Beta-lactamases such as ESBLs, AmpC, and carbapenemases are evaluated by diffusion disk testing when needed. The Resist-5 O.K.N.V.I column chromatography test (CORIS BioConcept, Gembloux, Belgium) is used to detect carbapenemase enzymes, including OXA-48-like. In addition, minimum inhibitory concentration (MIC) for colistin was determined by broth microdilution (ComASPTM Colistin, Liofilchem, Italy) and the molecular identification of OXA-48-like enzyme was carried out at the Biochemistry and Nutrition Research Center of the Universidad Nacional Mayor de San Marcos, Peru. Bacterial DNA was extracted by heat shock and multiplex polymerase chain reaction (PCR) amplification for the bla_{VIM}, bla_{IMP}, bla_{NDM}, $bla_{OXA\text{-}48\text{-}like}$, and bla_{KPC} genes following previously established conditions [8].

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2. Ethics statement

This study was approved by the INEN institution review board last January 27, 2022 with designated protocol number INEN 22-01. No informed consent from any patient was obtained since this study used laboratory test registers and patient medical records in obtaining data. Patient confidentiality was strictly upheld for the whole duration of this study.

RESULTS

Seven OXA-48-like CPE strains isolated from different patients were found. None of the patients had recent immigration or travel history. Most of the isolates (5/7) were recovered from patients hospitalized between 3 and 28 days. Inpatients (5/7) were treated with carbapenems, while outpatients and emergency admissions (2/7) had no history of treatment with this beta-lactam (**Table 1**). Also, two of the seven patients, who had prior meropenem monotherapy, remained after positive culture for OXA-48-like CPE until hospital discharge. Three of the five untreated patients, who had prior meropenem monotherapy, died before cultures were finalized, and two, who were outpatients, had not received prior therapy and had no medical prescription after culture. The etiology of OXA-48-like CPE was diverse with *Klebsiella* genera predominance (5/7). Notably, in all cases, the BD Phoenix automated system issued a MIC of ≥1 μg/mL for ertapenem and a MIC of >64/4 μg/mL for piperacillin/tazobactam. In addition, resistance category to imipenem and meropenem was found (2/7), at least one indeterminate category for any of these carbapenems (5/7), and other serine β-lactamases such as ESBLs (3/7) and AmpC (3/7). Disk diffusion testing ruled out the production of other carbapenemases and confirmed the presence of ESBL and AmpC (**Table 2**). Colistin susceptibility testing showed that all strains had a MIC ≤0.5 μg/mL Also, the antimicrobial sensitivity profile of the strains was compared, and it showed slight similarities among them (data not shown). The immunochromatographic study confirmed the presence of the OXA-48-like enzyme in all isolates while class A (*Klebsiella pneumoniae* carbapenemases [KPC]) and class B (New Delhi metallo-β-lactamases [NDM]; Verona integron-encoded metallo-β-lactamases [VIM]; and Imipenemases [IMP]) were ruled out for them. Finally, the multiplex PCR, for the five isolates that could be recovered, showed amplification for carbapenemase OXA-48-like with a 775 bp product, while none of the other carpabemases was amplified for class A (KPC) or class B (VIM, IMP, NDM) carbapenemase genes (**Fig. 1**). In addition, the finding of $bla_{\text{CTX-M}}$ gene confirmed the presence of ESBL in all isolates previously detected in the phenotypic study.

Table 1. Clinical and hospital characteristics of OXA-48-like CPE isolates

Isolates	U-1846	H-1969	H-2364	U-3697	S-1560	H-4379	U-10337
Age (years)/sex	51 / F	19 / F	47 / M	58 / F	12 / F	15 / M	28 / F
Isolation date	Mar/06/2021	Apr/09/2021	Apr/12/2021	May/09/2021	May/31/2021	Jul/18/2021	Nov/17/2021
Source	Urine	Blood	Blood	Urine	Bronchial fluid	Blood	Urine
Medical department	Outpatient	Hospitalization	Hospitalization	Hospitalization	Hospitalization	Hospitalization	Emergency
Oncology diagnosis	Renal cancer	ALL	ALL	Breast cancer	Ewing sarcoma	ALL	Epidermoid cancer
Reason for microbiology study	Control	Atypical pneumonia	Septic shock	HAIs	Septic shock	Septic shock	Genital bleeding
Prior carbapenem therapy	None	Meropenem	Meropenem	Meropenem	Meropenem	Meropenem	None
Outcome	None	Death	Hospital discharge	Hospital discharge	Death	Death	Hospital discharge
Risk factors	None	CVC, COVID-19	RD, MV, CVC, COVID-19	MV, CVC, COVID-19	MV	CVC, COVID-19	RD

CPE, Carbapenemase-producing *Enterobacteriaceae*; F, female; M, male; ALL, acute lymphoblastic leukemia; CVC, central venous catheter; COVID-19, Coronavirus disease 2019; HAIs, healthcare-associated infection; RD, renal disease; MV, mechanical ventilation.

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Table 2. Microbiological characteristics of OXA-48-like CPE isolates

Isolates	U-1846	H-1969	H-2364	U-3697	S-1560	H-4379	U-10337
Etiology	*Klebsiella pneumoniae*	*Klebsiella pneumoniae*	*Klebsiella aerogenes*	*Klebsiella aerogenes*	*Klebsiella aerogenes*	*E. coli*	*E. coli*
Ertapenem (μg/mL)	2 (R)	>1 (R)	>1 (R)	>2 (R)	>1 (R)	>1 (R)	>2 (R)
Piperacillin/tazobactam (μg/mL)	>64/4 (R)	>64/4 (R)	>64/4 (R)	>64/4 (R)	>64/4 (R)	>64/4 (R)	>64/4 (R)
Meropenem (μg/mL)	1 (S)	1 (S)	2 (I)	8 (R)	8 (R)	1 (S)	2 (I)
Imipenem (μg/mL)	2 (I)	2 (I)	2 (I)	8 (R)	4 (R)	2 (I)	4 (R)
Other resistance mechanisms[a]	None	None	AmpC	AmpC	ESBLs / AmpC	ESBLs	ESBLs

[a]AmpC detection was based on cefoxitin resistance in the antibiogram.
CPE, Carbapenemase-producing *Enterobacteriaceae*; R, resistance; S, susceptible; I, intermediate; ESBLs, Extended-spectrum beta-lactamases.

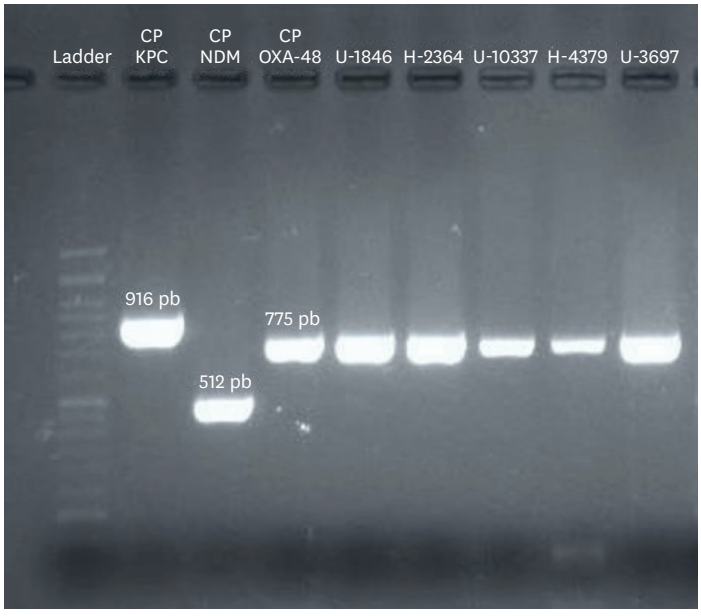

Figure 1. Agarose gel electrophoresis 1.5%. Ladder 100 bp; CP KPC: *Klebsiella pneumoniae* ATCC BAA-1705; CP NDM: *K. pneumoniae* ATCC BAA-2146; CP OXA-48: *K. pneumoniae* ATCC BAA-2524; U-1846, H-2364, U-10337, H-4379, U-3697: studied isolates.
CP KPC, *Klebsiella pneumoniae* carbapenemases positive control; CP NDM, New Delhi metallo-b-lactamases positive control; CP OXA-48, OXA-48-like positive control.

DISCUSSION

We highlight the appearance of OXA-48-like CPE in our center, which creates a new scenario for the laboratory detection and therapeutic management and constitutes a serious threat to cancer patients suffering from infections caused by these isolates [5]. To the best of our knowledge, until the date when the preliminary results of the study were presented, there were no official reports of OXA-48-like CPE isolates in our country.

The etiology and mortality rates in our study were similar to those in previous reports. *Klebsiella* spp. and *Escherichia coli* are the main *Enterobacteriaceae* producing OXA-48-like carbapenemase [4, 9]. However, other genera such as *Enterobacter, Citrobacter, Serratia* and *Morganella* were found harboring OXA-48-like enzyme [10–12], in studies with a higher number of analyzed cases. The mortality rate of infections by OXA-48-like CPE in our study was lower than that in other studies [4, 13–15]. However, this comparison could be inappropriate because those studies included cases with heterogeneous characteristics,

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considering the types of infections, mortality risk factors, and antimicrobial therapy, which are directly related to the worst outcome.

The finding of resistance to ertapenem (≥1 μg/mL) and piperacillin/tazobactam (>64/4 μg/mL) according to CLSI, in the absence of other carbapenemases, in all our isolates supports their potential usefulness as presumptive markers of OXA-48-like CPE [5, 6]. In addition, other markers for this enzyme have been proposed using EUCAST (European Committee on Antimicrobial Susceptibility Testing) criteria such as resistance to temocycline (>128 mg/mL or <11 mm) plus resistance to meropenem (≥0.5 μg/mL) or faropenem (with a zone of double inhibition) [10, 16], which perform good screening. Recently, resistance to ertapenem (2 - 4 μg/mL) and piperacillin/tazobactam (data not shown) was considered in this regard [17].

Some of our strains harbor multiple resistance mechanisms that may hinder antimicrobial action on isolates, leading to a greater probability of therapeutic failure using the involved antibiotics [18]. Multidrug resistance in these isolates due to the production of ESBLs and AmpC as well as possible impermeability may explain the heterogeneous *in vitro* sensitivity profile to carbapenems as well as the resistance and indeterminate categories for imipenem and meropenem [3, 19]. Moreover, this associated resistance could complicate the detection of OXA-48-like CPE in laboratories where there are no complementary tests to the antimicrobial susceptibility study. Furthermore, these difficulties may play a role in the hidden spread of this enzyme.

There is currently no consensus on the report of the antibiogram for OXA-48-like in CPE isolates. EUCAST and CLSI recommend reporting the susceptibility profile according to the antibiogram cut-off points, regardless of whether the isolate produces this carbapenemase. Therefore, most of our isolates categorized as susceptible or intermediate to imipenem and meropenem could be considered an alternative therapy for OXA-48-like CPE infections [17]. Similarly, in cases in which ESBLs were not detected, treatments based on broad-spectrum cephalosporins could be used safely. However, due to diverse responses in the treatment of OXA-48-like CPE infections, the therapeutic approach to these infections should be individualized based on antimicrobial susceptibility, the type and severity of the infection, and the infection characteristics in each patient [20].

Immunochromatographic test performance accords with what has been described as a reliable tool for the rapid and simple detection of OXA-48-like CPE. This methodology achieved higher sensitivity and specificity for detecting this enzyme in comparison with molecular detection by PCR. Therefore, it provides timely detection that can help prevent its dissemination such as hospital outbreaks [21, 22]. As a result, this test has been proposed as part of easy-to-implement diagnosis algorithms in the daily routine of a standard microbiology laboratory with limited access to molecular biology tools [16].

Most of the detected OXA-48-like CPE show a possible hospital origin, probably as a result of the previous and routine use of carbapenems in hospital practice. The administration of carbapenems in hospitalized patients as a prophylactic measure results in selective pressure, evolving resistance mechanisms such as OXA-48-like CPE [23, 24]. In contrast, isolates from patients without hospitalization history indicate its probable community acquisition, as described previously, which alerts us to the dissemination of this enzyme [25].

Molecular study allowed the definitive detection of OXA-48-like CPE, although the current emergence of this enzyme group, in which OXA-48 and OXA-163 are the most common,

requires identifying its variants. The eleven OXA-48 like variants known to date could differ in hydrolytic activity on carbapenems, geographical distribution, producing bacteria, and associated resistance mechanisms [4, 11]. We believe our isolates could not be genetically related due to the distant dates of strain isolation, the diverse origin of patients, the heterogeneity of associated resistance mechanisms, and little similarity in the antimicrobial susceptibility profile of strains. However, only molecular study at the clonal level would make it possible to confirm it, leading to a better understanding of the origin, dissemination, and molecular epidemiology associated with OXA-48-like CPE infections.

Antibiotic therapy for OXA-48-like CPE infections should base on non-beta-lactam families, although the presence of multiple resistance mechanisms and antibiotic availability must also be considered. Polymyxin, tigecycline and aminoglycosides could be the best options, although beta-lactams such as ceftazidime and meropenem could be included as part of the combined therapy in ESBL-negative and meropenem MIC ≤4 μg/mL cases [4].

In our center, *Enterobacteriaceae* harboring ESBL are frequently isolated and colistin has limited availability; therefore, ceftazidime is not a good option, and meropenem monotherapy is used regularly. Finally, the combination of colistin-based regimens [13] and new beta-lactamase inhibitors (BLIs) combined with proper beta-lactams such as ceftazidime-avibactam [26], seem to be the best current options to treat infections of OXA-48-like CPE.

Colistin is considered a last resort against infections caused by *Pseudomonas aeruginosa*, the *Acinetobacter baumannii* complex, and CPE. The dosing strategy of colistin to treat carbapenem-resistant organisms has been studied with promising results but with adverse effects. Recently, a study on carbapenem-resistant *Acinetobacter baumannii* in critically ill patients found that a loading dose of colistin methanesulfonate (300 mg followed by a maintenance dose of 150 mg every 12 h) improved the patient's survival rate. However, as it was found to be associated with an increase in nephrotoxicity, a minimum creatinine clearance level is required [27]. Combined therapies for carbapenem-resistant bacterial infections, including polymyxin, have been found to be elective therapies. Polymyxin-based combination therapy reduced mortality, but also in combination with meropenem [28, 29]. However, it had adverse effects on patients, including nephrotoxicity [30, 31].

Appropriate use of antibiotics is a key step in the fight against bacterial resistance emergence. Effective application of antimicrobial restriction systems in clinical settings leads to a decrease in the use of carbapenems and, consequently, reduces the carbapenem-resistance rate. It has also been associated with a decrease in the number of meropenem-resistant *Pseudomonas aeruginosa* isolates. However, more data must be analyzed to determine the impact of controlling prescriptions for carbapenem-resistant *Enterobacteriaceae* [32].

Antimicrobial resistance needs to be faced under the "one health" concept by considering the interdependence between humans, animals and the environment as potential infection sources of CPE. In this regard, continued education and surveillance of CPE are mandatory to prevent and control CPE transmission in hospitals, and it must involve the participation of all healthcare professionals who have direct or indirect contact with patients. Moreover, it is recommended that programs be implemented for research and epidemiological surveillance, increasing the participation of clinical laboratories by developing flowcharts and characterizing CPE. Surveillance cultures should also be performed according to the local epidemiology, as a tool for making decisions based on the generated data [33].

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Our study had some limitations, which encouraged the prospective evaluation of a larger sample size. It includes a small number of cases, as they are the first of emerging infections by CPE harboring OXA-48-like in our specialized center. In addition, we did not identify the variants within this OXA-48-like enzyme group or determine whether the isolates were genetically related; neither of these studies was performed because of our limited laboratory resources.

In conclusion, we confirm the emergence of OXA-48-like CPE isolates in our cancer center and emphasize the need to implement surveillance and detection measures, mainly at the molecular level, of these strains in order to control their dissemination.

We found practical and inexpensive methodologies for the detection of OXA-48-like CPE:

- The finding of resistance to ertapenem and piperacillin/tazobactam in the antibiogram in the absence of class A and B carbapenemases, for screening.
- Immunochromatographic study, for confirmation.

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