OXA-48 carbapenemase-mediated ceftazidime-avibactam resistance; first reported case in Saudi Arabia’s western region and review of literature

Yasser Al Dabbagh, Rola Hassan, Nezar Bahabri, Mohammed Qutub

ABSTRACT

Introduction: The emergence of carbapenemase-resistant Enterobacteriaceae (CRE) is an imminent threat to public health obligating, the development of novel β-lactam/β-lactamase inhibitors to combat its relentless spread, an example of which is ceftazidime-avibactam (CAZ-AVI). Since its introduction in 2015, worldwide data continues to pour in describing different mechanisms of treatment failure, primarily mediated by members of metallo-β-lactamase (MBL), Klebsiella pneumoniae carbapenemase (KPC), and oxacillinase (OXA) enzymes. Case Report: We report a case of a previously healthy 22-year-old male who was admitted to the critical care burn unit as a case of third-degree chemical burn injury involving 80% of his body surface area. His tissue cultures grew Klebsiella pneumoniae which was resistant to CAZ-AVI. Further analysis of resistance patterns by Xpert® Carba-R detected the presence of both NDM (New Delhi metallo-β-lactamase) and OXA-48 mutation genes. Conclusion: OXA-48-mediated carbapenemase resistance is a regional threat in the Middle East and it is increasingly expanding in terms of its epidemiology and activity against novel antimicrobials. This activity is primarily mediated by mutant doubling and plasmid adaptation and can be horizontally acquired by coexistence with other resistant genes. We are reporting the first OXA-48-mediated CAZ-AVI resistance in the western region of Saudi Arabia which raises the concern about CRE spread in the country. Necessitating wiser use of available genotypic testing coupled with strict adherence of infection control protocols and antimicrobial stewardship programs.

Keywords: Carbapenemase, Ceftazidime-avibactam, Enterobacteriaceae, OXA-48

INTRODUCTION

β-Lactamases are enzymes that deactivate the antibiotic’s protective ring, resulting in its ineffectiveness [1]. The Ambler classification system is the most widely used to categorize β-lactamases. It constitutes four classes: Classes A, B, C, and D. Class A consists of extended spectrum β-lactamases (ESBLs) and serine carbapenemase including KPCs. Class B comprises of MBLs including the NDMs, Verona integron-encoded
(VIM), and imipenemase (IMP). Class C includes AmpC β-lactamases while Class D is designated for oxacillinases including OXA-48 and OXA-48 like enzymes [2].

Carbapenemase-resistant Enterobacteriaceae (CRE) is a class of bacterial organisms that expresses carbapenemase resistance via three of the four aforementioned class subtypes (A, B, and D) [3]. Carbapenems had remained the cornerstone of treatment of highly resistant microorganisms, including ESBL, until the recent emergence of carbapenemases [4]. Efforts to combat this new threat to public health had led to the introduction of novel antibiotics, including CAZ-AVI [5].

Ceftazidime is a widely used third generation cephalosporin which is mainly active against gram-negative organisms. Avibactam, on the other hand, is a new synthetic inhibitor of β-lactamases with strong activity against Classes A (e.g., KPC), C (e.g., AmpC β-lactamases), and D (e.g., OXA-48) but not class B (MBL, including NDM, VIM, and IMP) [6, 7].

The expanding use of CAZ-AVI in CRE infections due to its in vitro activity, its safety profile and the lack of effective alternative regimens will inevitably subject it to rising resistance rates [8]. As a part of the International Network for Optimal Resistance Monitoring (INFORM) global surveillance study, 92.5% of OXA-48 producing Enterobacteriaceae were susceptible to CAZ-AVI. The susceptibility increases to 99.2% with MBL negative isolates [9].

Following CAZ-AVI’s recent introduction into the Saudi health care system, a case series was published in Riyadh in 2018 documenting the resistance spectrum that had developed in response to exposure to the new drug. The only case included that was resistant to CAZ-AVI was harboring both OXA-48 and NDM enzymes [10].

To the best of our knowledge, this is the first published case of a CRE strain showing OXA-48-mediated resistance to CAZ-AVI in Saudi Arabia’s western region. This raises a grave concern regarding the accelerated rates of resistance to newly introduced antibiotics and suggests the need for more stringent efforts in studying resistance spectra.

CASE REPORT

We are reporting the case of a 22-year-old male who was not known to have any previous chronic medical illnesses. He was admitted to the critical care burn unit as a case of chemical burn injury after his uniform caught fire near a burning zinc tank.

On initial presentation the patient was conscious, oriented to time, place, and person. He was afebrile, however hypertensive and tachycardic. He was in severe pain with a score of 8 out of 10. His third-degree burns involved 80% of his body surface area, including the right side of his face, both his entire upper and lower limbs, his trunk, and back.

After initial stabilization by the intensive care unit team, the patient was sent to the operation theatre to undergo an urgent fasciotomy of the right lower limb wound and of another wound in the dorsum of his right foot. An escharotomy of the right upper limb was also done on the lateral side. His perioperative course was complicated by septic shock and he was returned to the intensive care unit intubated, mechanically ventilated, and reliant on vasopressors.

The tissue culture obtained intraoperatively grew Klebsiella pneumoniae which was resistant to β-lactams, cephalosporins, carbapenems, fluoroquinolones, gentamicin, and CAZ-AVI—but was susceptible to amikacin and tigecycline (Table 1).

Further analysis of resistance genotyping by Xpert® Carba-R (Cepheid, USA) which is a real-time polymerase chain reaction assay for rapid detection and differentiation of five genes (blaKPC, blaVIM, blaOXA-48, blaIMP-1, and blaNDM) responsible for carbapenem resistance, detected the presence of both NDM and OXA-48 mutation genes. The patient was thus referred to the infectious diseases team and after review of his susceptibility results, the patient was started on tigecycline (100 mg intravenously initially, then 50 mg intravenously every 12 hours) in place of meropenem (1000 mg intravenously every eight hours) and vancomycin (1500 mg intravenously initially as loading dose, then 1000 mg intravenously every eight hours), which he initially received (Table 2).

Table 1: Klebsiella pneumoniae isolate antimicrobial susceptibility test in our case—showing resistance to ceftazidime-avibactam and sensitivity only to amikacin and tigecycline

<table>
<thead>
<tr>
<th>Antimicrobial</th>
<th>MIC</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ampicillin</td>
<td>≥ 32</td>
<td>Resistant</td>
</tr>
<tr>
<td>Amoxicillin/clavulanic acid</td>
<td>≥ 32</td>
<td>Resistant</td>
</tr>
<tr>
<td>Piperacillin/tazobactam</td>
<td>≥ 128</td>
<td>Resistant</td>
</tr>
<tr>
<td>Cefalotin</td>
<td>≥ 64</td>
<td>Resistant</td>
</tr>
<tr>
<td>Cefoxitin</td>
<td>≥ 64</td>
<td>Resistant</td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>≥ 64</td>
<td>Resistant</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>≥ 64</td>
<td>Resistant</td>
</tr>
<tr>
<td>Cefelime</td>
<td>≥ 64</td>
<td>Resistant</td>
</tr>
<tr>
<td>Imipenem</td>
<td>≥ 16</td>
<td>Resistant</td>
</tr>
<tr>
<td>Meropenem</td>
<td>≥ 16</td>
<td>Resistant</td>
</tr>
<tr>
<td>Amikacin</td>
<td>4</td>
<td>Sensitive</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>≥ 16</td>
<td>Resistant</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>≥ 4</td>
<td>Resistant</td>
</tr>
<tr>
<td>Tigecycline</td>
<td>2</td>
<td>Sensitive</td>
</tr>
<tr>
<td>Nitrofurantoin</td>
<td>256</td>
<td>Resistant</td>
</tr>
<tr>
<td>Trimethoprim/sulfamethoxazole</td>
<td>≥ 320</td>
<td>Resistant</td>
</tr>
<tr>
<td>Ceftazidime-avibactam</td>
<td>≥ 8</td>
<td>Resistant</td>
</tr>
</tbody>
</table>

MIC: Minimal inhibitory concentration
On the fifth day of the patient’s presentation to our hospital’s emergency department, he passed away as a consequence of septic shock due to his overwhelming burns.

**DISCUSSION**

Ceftazidime-avibactam offers a significant advantage over previously developed antimicrobials with in vitro activity against CRE, such as colistin, gentamicin, and tigecycline, which are limited by concerns over efficacy and toxicity. In recent studies, CAZ-AVI is superior to other treatment regimens against carbapenem-resistant *Klebsiella pneumoniae* as it improved clinical outcomes, decreased all-cause hospital mortality rate, and improved benefit-risk outcomes [11–13].

After the approval of CAZ-AVI in 2015 by the U.S. Food and Drug Administration for the treatment of CRE [14], cases from all over the world had reported treatment failure, which in some studies had reached up to 30% [15]. The data was variable, inconsistent, and according to recent studies, suggestive of possible regional variations in its mechanisms of resistance [16].

Shortly after the drug’s introduction in 2015, Humphries et al. from the United States reported the first clinical KPC-3-isolates resistant to CAZ-AVI [17]. Another published report from the United States in 2017 comes from Giddins et al. who reported the emergence of CAZ-AVI resistance in *Klebsiella pneumoniae* due to the presence of the KPC-2 resistance gene [18]. In the same year, Both et al. from Germany reported resistance in a clinical *Klebsiella pneumoniae* isolate which produced OXA-48 [19]. Following the plethora of reported data, it was found that the emergence of resistance to CAZ-AVI is mostly seen in KPC-3-producing organisms and more rarely in KPC-2- or OXA-48-producing *Klebsiella pneumoniae* [20].

The first OXA-48-producing *Klebsiella pneumoniae* strain was isolated in Turkey in 2001 [21]. OXA-48-producing isolates are increasingly identified in many parts of the world and are dominating in certain regions, such as the Middle East and North Africa [3].

Recent studies reported that both CAZ and CAZ-AVI exposure resulted in amino acid substitutions in OXA-48 that compromised its carbapenemase and penicillinase activities by the occurrence of single (OXA-48:P68A) and double (OXA-48:P68A,Y211S) gene substitutions. Those substitutions, as demonstrated by X-ray crystallography structures, lead to increased flexibility within the OXA-48 structure, likely contributing to elevated CAZ hydrolysis. Furthermore, molecular modeling of double substituted OXA-48 gene showed altered H-bond network which caused higher CAZ resistance and loss of interaction if aromatic stacking that stabilized AVI binding, which, in consequence, decreased AVI inhibitory effect. Other important mechanism of OXA-48 resistance is plasmid adaptation to CAZ and CAZ-AVI which deliberated a significant fitness cost as well as loss of stability [22].

Although it is confirmed in literature that MBL positive isolates are naturally resistant to CAZ-AVI, OXA-48 positivity in relation to MBL was only recently recognized. A possible theory is that plasmid harboring gene resistance can be transferred between bacteria within the same species or between different species via conjugation (i.e., the passing on of the resistance genes). Further studies are needed to understand the mechanism of resistance acquisition in clinical practice, as many papers, including the INFORM surveillance had studied only in vitro patterns of resistance [9, 20, 23].

Strict implementation of an antibiotic stewardship in conjunction with the use of well-established genotypic methods is imperative for prescribing efficient β-lactamases/carbapenemases and decreasing its resistance burden [24].

**CONCLUSION**

OXA-48-mediated carbapenemase resistance is a regional threat in the Middle East and it is increasingly expanding in terms of its epidemiology and activity against novel antimicrobials. This activity is primarily mediated by mutant doubling and plasmid adaptation and can be horizontally acquired by coexistence with other resistant genes. We are reporting the first OXA-48-mediated CAZ-AVI resistance in the western region of Saudi Arabia which raises the concern about CRE spread in the country. Necessitating wiser use of available genotypic testing coupled with strict adherence of infection control protocols and antimicrobial stewardship programs.

**REFERENCES**


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Author Contributions

Yasser Al Dabbagh – Design of the work, Drafting the work, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Rola Hassan – Acquisition of data, Drafting the work, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved


Yasser Al Dabbagh – Design of the work, Drafting the work, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Mohammed Qutub – Analysis of data, Interpretation
of data, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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**Conflict of Interest**
Authors declare no conflict of interest.

**Data Availability**
All relevant data are within the paper and its Supporting Information files.

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