Report of β-lactam antibiotic–induced vancomycin-resistant
Staphylococcus aureus from a university hospital in Egypt

A. E. Taha1,2, M. F. Badr1, F. E. El-Morsy2 and E. Hammad2
1) Microbiology and Immunology Unit, Department of Pathology, College of Medicine, Jouf University, Al-Jouf, Saudi Arabia and 2) Medical Microbiology and Immunology Department, Faculty of Medicine, Mansoura University, Mansoura, Egypt

Abstract

We report a case of hospital-acquired pneumonia that to our knowledge is the first description in Egypt of the emergence of vancomycin (VA)-resistant Staphylococcus aureus due to the concomitant use of β-lactams. The combination of β-lactam antibiotics and VA in the treatment of methicillin-resistant S. aureus must be avoided to refrain from inducing VA resistance; further, if there is coinfection with Gram-negative bacilli, β-lactams must be avoided. If β-lactam antibiotic–induced VA-resistant methicillin-resistant S. aureus is isolated, then β-lactams must be avoided until the organism’s sensitivity to VA is restored if VA is the only therapeutic option available. © 2019 The Authors. Published by Elsevier Ltd.

Keywords: BIVR, MRSA, Staphylococcus aureus, Vancomycin resistance, β-lactams

Original Submission: 25 October 2018; Revised Submission: 23 December 2018; Accepted: 15 January 2019

Article published online: 30 January 2019

Case presentation

A 50-year-old comatose woman was referred by another hospital to the intensive care unit of the emergency department at Mansoura University Hospital after a bad car accident. At arrival she had been receiving VA/imipenem empirical therapy for 5 days, but she had fever, leukocytosis and chest infection for which endotracheal aspirate was collected as previously described [3].

After ethical approval was obtained from the hospital’s management board, MRSA was isolated as a pure growth by using classical bacteriologic methods [4] in the microbiology diagnostics and infection control unit in the microbiology and immunology department. MRSA was then identified by biochemical reactions [5], cefoxitin-based disc diffusion method according to Clinical and Laboratory Standards Institute criteria [6] and confirmed by MecA gene amplification PCR [7]. VA resistance (MIC = 32 μg/mL) of the isolate was detected as previously described [8].

Because the patient was receiving empirical therapy with VA/imipenem, the organism was suspected to be BIVR. Confirmation was done by phasing out treatment and performing VA MIC testing. The phasing-out test of the BIVR phenomenon was
done as described elsewhere [2]. Briefly, the isolate was transferred to antibiotic-free Müller-Hinton agar, and the plate was incubated at 37°C for 24 hours. Bacterial suspensions from the plate were inoculated again on antibiotic-free Müller-Hinton agar and incubated for 24 hours at 37°C. This serial transfer and culture was repeated for 5 successive days. Then the VA MIC test was performed again. This time, the organism became sensitive to VA (MIC = 2 μg/mL).

The VRSA isolate reported in the current study showed multidrug resistance to penicillin, amoxicillin/clavulanic, ampicillin/sulbactam, cefazolin, cefuroxime, gentamicin and ciprofloxacin by the disc diffusion method but was sensitive to LZD. The patient was treated with LZD (targeting VRSA) and colistin (targeting carbapenem-resistant Klebsiella pneumoniae). After 2 weeks, the patient’s clinical condition had improved; all signs of infection subsided, chest X-ray became normal and LZD/colistin therapy was stopped. The patient was transferred to a ward.

**Discussion**

The widespread use of VA to treat MRSA infections and other Gram-positive cocci has led to the appearance of different degrees of VA resistance. The first strain of *S. aureus* with reduced susceptibility to VA was reported from Japan in 1997, whereas VRSA isolates were first reported from the United States, Brazil and Jordan in 2002 [9].

BIVR is a subtype of MRSA that shows VA resistance only in the presence of β-lactam antibiotics, meaning that the synergistic effect of β-lactams and VA on MRSA does not occur. The BIVR mechanism was tested as previously described [2]. The multidrug-resistant nature of the organism has been previously reported [10].

Nosocomial infections caused by BIVRs represent a crucial challenge for hospital infection control, antimicrobial susceptibility testing and antimicrobial therapy because these organisms are resistant to most antibiotics. The data above indicate that hospital administrators should strengthen optimal antibiotic use according to local hospital policy, and the therapy chosen to treat infections should be based on *in vitro* antibiotic sensitivity tests.

Our results emphasize that clinicians must avoid the combination of β-lactam antibiotics and VA in the treatment of MRSA to avoid inducing VA resistance. Further, if there is co-infection with Gram-negative bacilli, β-lactams must be avoided. If BIVRs are isolated, β-lactams must be avoided for 5 successive days until the organism’s sensitivity to VA is restored. If the organism is resistant to all other antibiotics, then VA can be tried.

**Conflict of interest**

None declared.

**References**

[1] Antonanzas F, Lozano C, Torres C. Economic features of antibiotic resistance: the case of methicillin-resistant *Staphylococcus aureus*. Pharmacoeconomics 2015;33:325–325.
[2] Hirao Y, Ikeda-Dantsuji Y, Matsui H, Yoshida M, Hori S, Sunakawa K, et al. Low level β-lactamase production in methicillin resistant *Staphylococcus aureus* strains with β-lactam antibiotics-induced vancomycin resistance. BMC Microbiol 2012;12:69.
[3] Campos JM, McNamara AM, Howard BJ. Specimen collection and processing. In: Howard BJ, Kreise JF, Weissfeld AS, Smith TF, Tilton RC, editors. Clinical and pathogenic microbiology. Philadelphia: CV Mosby; 1994. p. 213–42.
[4] Cheesbrough M. Microbiological tests. In: Cheesbrough M, editor. District laboratory practice in tropical countries. Cambridge: Cambridge University Press; 2006. p. 62–70.
[5] Forbes BA, Sahn DF, Weissfeld AS. *Staphylococcus*, *Micrococcus* and similar organisms. Bailey and Scott’s diagnostic microbiology. 12th ed. New York: Elsevier; 2007.
[6] Clinical and Laboratory Standards Institute. Performance standards for antimicrobial susceptibility testing. Twenty-fourth informational supplement. CLSI document M100-S24. Wayne, PA: Clinical and Laboratory Standards Institute; 2014.
[7] Aushbel F, Brent R, Kingston R, Moore D, Seidman J, Smith J, et al. Preparation of genomic DNA from bacteria. In: Aushbel F, Brent R, Kingston R, Moore D, Seidman J, Smith J, et al., editors. Current protocols in molecular biology. New York: Wiley; 1990. p. 241.
[8] Sarker SD, Nahar L, Kumarsamy Y. Microtitre plate based antibacterial assay incorporating resazurin as an indicator of cell growth, and its application in the *in vitro* antibacterial screening of phytochemicals. Methods 2007;42:321–4.
[9] Al-Obeid S, Haddad Q, Cherkaoeu A, Schrenzel J, Francois P. First detection of an invasive *Staphylococcus aureus* strain (D958B) with reduced susceptibility to glycopeptides in Saudi Arabia. J Clin Microbiol 2010;6:2199–204.
[10] Peacock SJ, Paterson GK. Mechanisms of methicillin resistance in *Staphylococcus aureus*. Annu Rev Biochem 2015;84:577–601.