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

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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.

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

The most effective antibiotics against methicillin-resistant *Staphylococcus aureus* (MRSA) are vancomycin (VA) and linezolid (LZD) [1]. MRSA-infected patients are commonly coinfected with Gram-negative bacilli that are naturally resistant to VA and LZD. In such conditions, treatment with a combination of VA with one of the β-lactams has been used in the past, depending on pharmacologic synergy. However, antagonism was increasingly detected in the form of MRSA isolates that become resistant to VA only in the presence of β-lactam antibiotics [2].

We present a case of hospital-acquired pneumonia caused by β-lactam antibiotic–induced VA-resistant MRSA (BIVR) and *Klebsiella pneumoniae*. To our knowledge, this is the first description of the emergence of VA-resistant *S. aureus* (VRSA) due to the concomitant use of β-lactams in Egypt.

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

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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 administers 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.

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