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Case Report

Treatment Strategies for Persistent and Complicated MRSA Bacteremia Under Vancomycin Monotherapy, (Case Report)

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Abstract

Usually, combination therapy is associated with a shorter time to blood sterilization than vancomycin monotherapy for persistent MRSA bacteremia. Here we report a case of a 71-year-old female patient who originally had high comorbidity and systemic complications (cardiac, kidney, and pulmonary diseases), and she previously had a bilateral total knee replacement. Recently, the patient admitted on the 4th of January with sepsis, and MRSA was isolated from blood cultures drawn on the day of admission. The blood drawing on days 5, 9, 15, and 19, they remained positive for MRSA despite the monotherapy with vancomycin or linezolid. After 22 days, on the 26th of January, the patient expired. This case report supports the idea that a combination of vancomycin with other antibiotics like rifampicin, fosfomycin and/or an aminoglycoside are of the utmost importance to prevent treatment failure and as salvage therapy for persistent and complicated MRSA bacteremia.

Keywords: *MRSA Bacteremia; Vancomycin Monotherapy*

Background

Methicillin-resistant *Staphylococcus aureus* (MRSA) can cause a variety of infections, including skin and soft tissue infections, bacteremia, endocarditis, osteomyelitis, and fatal pneumonia [1,2]. MRSA infections are classified as community-acquired (CA-MRSA) or hospital-acquired (HA-MRSA) [3,4]. MRSA infection is associated with higher mortality than methicillin-sensitive *S. aureus* (MSSA) [5,6], and delay in antimicrobial therapy can further worsen the outcomes. In the last decade, rates of CA-MRSA infection have increased steadily, while HA-MRSA infection rates have generally declined [7]. CA-MRSA can acquire drug resistance genes, and their resistance to antibiotics has increased over time, making CA-MRSA treatment challenging. A retrospective study showed that, out of a total of 208 children, 136 (65.5%) cases of Methicillin-resistant *Staphylococcus aureus* were identified. Underlying diseases like; persistent bacteremia, sepsis at the time of admission, a secondary source of infection, admission to the intensive care unit, and surgery requirements were observed, and twelve patients (6%) died [8]. Several reports from different countries showed that, since the early 2000s, MRSA's worldwide prevalence has estimated at 25 - 50% [9]. Even with the ongoing development of new antibiotics and advances in infection prevention, MRSA

remains a challenging pathogen with persistently high mortality [10]. The mortality rate of systemic infections caused by MRSA is more than 50% [3,11], and the treatment failure rate of complicated MRSA bloodstream infections may be as high as 40% [12]. The prognosis of single-site MRSA infections is better, although multiple-site infections caused by MRSA are rare, difficult to treat, and associated with high mortality rates. Here, we report the case of a 71-year-old woman who presented to our institution with orthopnea and fatigue with sepsis for evaluation of a progressive increase in generalized edema. The patient did not respond to monotherapy either with vancomycin or linezolid or with a (too late) combination of vancomycin and clindamycin. The patient died 20 days after admission, having suffered from complicated bacteremia. The patient had high comorbidity (type 2 diabetes), an unknown source of infection, and previously had a total left knee replacement. MRSA was isolated from two sites, and the bacteremia persisted and never cleared. The previous factors were associated with an increased risk of failing bacteremia treatment. This high-risk case of complicated bacteremia showed a high rate of treatment failure because she was treated as a case of uncomplicated bacteremia, with vancomycin or linezolid alone. For decades, vancomycin has been the mainstay in treating MRSA infections and the drug of choice for treating MRSA bacteremia. However, vancomycin treatment failures are occasionally observed with some strains that are considered susceptible to vancomycin according to Clinical and Laboratory Standards Institute breakpoints (vancomycin minimum inhibitory concentration [MIC] ≤ 2 μg/mL). A recent international study showed that if an elevated vancomycin MIC (i.e. 1 - 2 μg/mL) in the susceptible range is obtained in routine testing, an alternative second method should be used for confirmation and to aid antibiotic therapy recommendations [13]. Vancomycin-resistant *S. aureus* (VRSA), vancomycin-intermediate *S. aureus* (VISA), and heterogeneous VISA (hVISA) are subject to vancomycin treatment failure. However, bacteremia caused by MRSA with reduced vancomycin susceptibility (VISA-RVS and hVISA), frequently resulted in treatment failure and mortality. The significance of the hVISA phenotype for treatment response and outcomes in patients with bacteremia has been addressed in previous studies, which showed that combination therapy with vancomycin and source of infection diagnosis for the management of vancomycin treatment failure should be considered [14]. Systematic screening may soon become necessary for infection control practices when glycopeptides are used.

Case Report

On the 4th of January 2022, a 71-year-old female patient was presented to our institution with a 38-degree fever, a heart rate of 80 bpm, a pulse of 67 per minute, a BP of 121/58 mm of Hg, no chest pain, and no clear consolidation according to a chest X-ray. The patient was suffering from orthopnea, fatigue, and a progressive increase in generalized edema. She was admitted on the same day. An echocardiogram (ECHO) performed one day after admission showed severe tricuspid valve regurgitation (TR), an ejection fraction (EF) of 65%, and a dilated and non-collapsing inferior vena cava (IVC). The patient was suffering from low-grade aortic valve stenosis (AVS), pulmonary hypertension (PHT), congestive heart failure (CHF) (predominantly right side), and acute kidney injury in chronic kidney diseases (AKI on CKD); the patient was voiding urine freely. The patient was a type 2 diabetic, and she had had a total knee replacement in the past. The patient was considered unfit for a trans-oesophageal echocardiogram (TOE) to be performed for her to determine if there was vegetation, though a TOE done 2 weeks prior showed no vegetation. Lab results on the day of admission showed: WBC (12.5, 14.2 and 109/L), CRP 200 mg/l, and PCT 1.6 ng/ml. The patient was septic and diagnosed with right-sided heart failure. On the day of admission (4th of January 2022), three sets of blood cultures were collected before administering ceftriaxone 1.5 g/q 6h intravenously as empirical treatment. After 18h, a positive blood culture was obtained using the BacT/Alert 3D system (bioMérieux) and clusters of gram-positive cocci were seen by gram staining. Sub-cultured and direct antimicrobial susceptibility testing from blood culture was performed using the Kirby-Bauer disc diffusion method, and the isolates were shown to be susceptible to all antibiotics tested except for oxacillin, trimethoprim, and levofloxacin. The empirical treatment was stopped, and vancomycin 1 gm Q 12 IV was started on the 5th of January. The identity of the isolate was confirmed as *S. aureus* by VITEK-MS, and its susceptibility was determined using the VITEK-2 system, which showed the same results as those obtained by the Kirby-Bauer disc diffusion method. The isolate was MRSA, and the MIC for vancomycin was 0.5 μg/mL, which was also confirmed by an E-test. Vancomycin treatment continued for nine days. Serum concentrations of vancomycin were monitored to maintain trough levels of 15 to 20 μg/ml and a blood culture was done every 48h. Under these conditions, MRSA

was persisting and growing in blood cultures. After one week of vancomycin treatment, the same MRSA was isolated from a swab taken from a wound on the left leg. On the 13th of January, the vancomycin was replaced by linezolid, 600 mg BD Q 12, also continuous for 10 days. Under linezolid treatment, blood cultures continued to show growth. On the 24th of January, linezolid was stopped, and the patient received vancomycin and clindamycin as another option. After 2 days, on the 26th of January, the patient expired.

Discussion

Clinical and microbiologic failures are common when treating bacteremia associated with complications, such as infective endocarditis and those present in our case, which lead to worse clinical outcomes, including longer hospitalizations and increased mortality. Here, we report and discuss the failed treatment of a complicated MRSA bacteremia case in a 71-year-old female initially treated by vancomycin, then by linezolid, as monotherapies. The patient was admitted with sepsis and covered by ceftriaxone as an empirical treatment. MRSA was isolated from blood culture, resistant only to oxacillin, trimipramine, and levofloxacin and sensitive to vancomycin, linezolid, clindamycin, gentamycin, moxifloxacin, rifampicin, tetracycline, and tigecycline, with MICs of 0.5, 2, 0.25, 0.5, 2, 0.5, 1, 0.12 µg/mL, respectively. As the patient had been admitted to the hospital before, and because the same MRSA strain was isolated from a wound on the left leg, we can conclude that the source of infection was a biofilm of MRSA that formed on the prosthesis and persisted for long periods. Treating such an infection represents a huge challenge because of the biofilms' high tolerance to antibiotics and their ability to evade the immune system [13]. For these reasons, bacteremia could be considered a nosocomial infection caused by HA-MRSA. Actually, and herein, we reported the susceptibility of all antibiotics tested because of the coexistence between CA-MRSA and HA-MRSA in community and hospital settings for better treating the infection. The patient had high comorbidity and systemic complications (cardiac, kidney, and pulmonary diseases), and she previously had a total knee replacement. These reasons could explain the severe infection in this patient and the treatment failure. In this case of MRSA bacteremia, monotherapy with vancomycin, linezolid, other anti-MRSA drugs, or the late combination of vancomycin with another synergistic antibiotic, were not the right treatments for such cases of bacteremia. Vancomycin has long been considered the first-line antibiotic treatment for invasive MRSA infection, including both HA-MRSA and CA-MRSA, however, in the case of this bacteremia patient, the vancomycin treatment was a failure (the blood culture persistently showed growth of MRSA and the strain was highly sensitive to vancomycin MIC 0.5 mg/l). According to an international study, this strain could not be hVISA and was not the reason for treatment failure [14,15]. Many shortcomings, such as the slow bactericidal activity of vancomycin, reduced activity against biofilm-forming pathogens, and poor tissue penetration play a possible role in the treatment failure [16]. Treatment failures often occur because trough levels of vancomycin can reach the subtherapeutic level, below the guideline recommendation of 15 - 20 ug/ml; however, in this patient, the level never went below this range [17]. As per clinical practice guidelines for the treatment of MRSA bacteremia, we started linezolid after vancomycin treatment failure. In this case, we found that vancomycin and linezolid as monotherapies, and even the late combination of vancomycin with clindamycin, were failed treatments. The patient expired after 2 days of the last option of treatment (combination of vancomycin with clindamycin). In this case, we should highlight the need for awareness of MRSA infection, the need for accurately diagnosing and identifying the source of infection, and the need for appropriate antibiotic guidelines and, if needed, surgical management. Antibacterial treatment should be adjusted not only according to the culture results but also according to the patient's history, severity of infection, and clinical response to treatment. *S. aureus* colonizes both artificial and tissue surfaces in humans, causing chronic infections that are difficult to cure. In this case, the patient had an old implant knee replacement, and MRSA was isolated from a wound on the left leg. Because biofilms can persist for long periods, months to years, we think that the source of infection could have been MRSA biofilm from the old implant knee replacement that was never cleared by the host's immune responses or antibiotic therapy, and these bacteria can disperse from the biofilm and enter circulation, resulting in bacteremia [18,19]. Also, we cannot exclude that the different lines, such as a hemodialysis catheter's central line or cannula, were the source of MRSA infection and bacteremia. In the United States, 40 - 50% of *S. aureus* strains are a major cause of infective endocarditis (IE), and biofilm *S. aureus* (vegetation particles) can then replicate on damaged valvular endothelium and disseminate (embolization) to cause systemic disease, resulting in complications such as congestive heart failure, sepsis, and persistent bacteremia [20]. In this patient, we cannot exclude the presence of infective endocarditis

(IE), even though a transesophageal echocardiogram (TOE) done 2 weeks after admission showed no vegetation, especially since she was treated for MRSA bacteremia using vancomycin and then linezolid as monotherapy for nine and ten days, respectively. In this case, if the diagnosis is still uncertain, further cardiac imaging should be considered [21]. The patient history and clinical examination showed that this patient suffered from complicated bacteremia (high comorbidity, source of infection never diagnosed, and persistent MRSA bacteremia). In this case, monotherapy treatment with vancomycin or linezolid, and even a late combination of vancomycin with clindamycin, led to treatment failure. In future cases like this one, combination therapy should be considered as the initial treatment.

Conclusion

Vancomycin MIC may not be an optimal sole indicator of vancomycin treatment failure in MRSA bacteremia [22]. A patient with high comorbidity (pulmonary, heart, kidney, type 2 diabetes, and had old prosthesis) may be the principal cause of treatment failure [23]. Management of patients with complicated MRSA bacteremia preferably needs to be provided by an infectious diseases and stewardship team consultation, including a standardized diagnostic work-up and therapeutic guidelines to improve treatment quality and patient outcomes. Anti-MRSA antibiotics, e.g. vancomycin or linezolid, should not be used as monotherapy. To prevent treatment failure, a combination of vancomycin with rifampicin, fosfomycin, and/or an aminoglycoside is of the utmost importance [24]. As per the IDSA, MRSA guidelines, the persistence of bacteremia after 2 - 4 days is one of the criteria for complicated bacteremia and thereby necessitating at least 4 - 6 weeks of treatment. Finally, treatment strategies must take into consideration recent exposure, source control, available synergy, and clinical data [25].

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