Scholars Journal of Medical Case Reports
Abbreviated Key Title: Sch J Med Case Rep
ISSN 2347-9507 (Print) | ISSN 2347-6559 (Online)
Journal homepage: https://saspublishers.com

OPEN ACCESS

Microbiology

First Case of Vancomycin-Resistant *Staphylococcus aureus* Infection Isolated in Marrakech, Morocco

H. El Fouar[1]*, W. Ait Driss[1], R. El Fargani[1], M. Idalene[1], N. Soraa[2], N. Tassi[1]

[1]Department of Infectious Diseases, University Hospital Center (CHU) Mohammed VI, Marrakech, Faculty of Medicine and Pharmacy FMPM, Cadi Ayyad University, Marrakech 40000, Morocco
[2]Department of Microbiology, University Hospital Center (CHU) Mohammed VI, Faculty of Medicine and Pharmacy FMPM, Cadi Ayyad University 40000 Marrakech, Morocco

DOI: https://doi.org/10.36347/sjmcr.2025.v13i05.009 | **Received:** 05.03.2025 | **Accepted:** 11.04.2025 | **Published:** 02.05.2025

***Corresponding author:** H. El Fouar
Department of Infectious Diseases, University Hospital Center (CHU) Mohammed VI, Marrakech, Faculty of Medicine and Pharmacy FMPM, Cadi Ayyad University, Marrakech 40000, Morocco

Abstract **Case Report**

Methicillin-resistant Staphylococcus aureus (MRSA) is well recognized as a major cause of healthcare-associated infections, but more concerningly, it is now emerging in the community, posing a growing threat to public health. Glycopeptides, particularly vancomycin, have traditionally been the cornerstone of MRSA treatment. However, their overuse has led to the emergence of vancomycin-intermediate and vancomycin-resistant *S. aureus* (VISA and VRSA, respectively). Although the underlying mechanisms of vancomycin resistance are not yet fully understood, it is believed that modifications in the bacterial cell wall, the site of action of glycopeptides, are crucial. Recent evidence also suggests that genetic material transfer between bacteria may contribute to the development of VRSA. Risk factors for VRSA development include advanced age, lower limb venous insufficiency, chronic ulcers, diabetes, and end-stage renal failure requiring hemodialysis. The spread of MRSA from hospital to community settings, along with the emergence of VISA and VRSA, has become a major concern among clinicians and microbiologists. The limited therapeutic options for these infections highlight the urgent need for new classes of antimicrobial agents. The number of VISA and VRSA infections is likely underestimated due to the limitations of both automated and non-automated detection methods. For clinical and public health reasons, it is essential that microbiology laboratories adequately test for vancomycin resistance in *S. aureus*. In this article, we report the first case of vancomycin-resistant *S. aureus* isolated at the CHU Mohammed VI in Marrakech in a patient hospitalized in the infectious diseases department for the management of multifocal tuberculosis complicated by acute renal failure at the hemodialysis stage. The patient responded well to treatment with linezolid and gentamicin, leading to complete resolution of symptoms.

Keywords: *Staphylococcus Aureus*, Antibiotic Resistance, vancomycin, VISA, VRSA.

1. INTRODUCTION

Infection caused by methicillin-resistant *Staphylococcus aureus* (MRSA) represents a global threat to public health. Vancomycin remains one of the first-line drugs for treating MRSA infections. However, *S. aureus* strains with complete resistance to vancomycin have emerged in recent years. Vancomycin-resistant *S. aureus* (VRSA) is mediated by the vanA gene cluster, which is transferred from vancomycin-resistant enterococci. Since the first VRSA isolate was recovered in Michigan, USA, in 2002, 52 VRSA strains have been isolated worldwide [1].

In this article, we report the first case of vancomycin-resistant *S. aureus* isolated at the CHU Mohammed VI in Marrakech.

2. OBSERVATION

We present the case of a 25-year-old patient, born and residing in Morocco, with no significant medical history, who was admitted to the infectious diseases department at CHU Mohammed VI in Marrakech for the management of multifocal tuberculosis complicated by acute renal failure requiring hemodialysis. The diagnosis of miliary tuberculosis was confirmed by GeneXpert testing of sputum samples, and renal involvement was confirmed by renal biopsy, which revealed tubulointerstitial damage and acute tubular necrosis.

During his 10-day hospitalization, the patient developed signs of sepsis originating from the

hemodialysis catheter, presenting with chills, fever (40°C), tachycardia (116 bpm), polypnea (32 breaths/min), and purulent discharge at the catheter site. A series of blood cultures were performed in both aerobic and anaerobic media, adhering to aseptic procedures, and the hemodialysis catheter was sent to the laboratory for cytobacteriological examination.

Biological assessment revealed anemia (7.7 g/dl), leukocytosis (11,290/mm³) with neutrophil predominance (10,150/mm³), lymphopenia (790/mm³), and moderately elevated C-reactive protein (CRP) levels (51 mg/ml). Blood cultures isolated a methicillin-resistant *Staphylococcus aureus* (MRSA) strain with reduced susceptibility to glycopeptides. The antibiotic susceptibility results are presented in Table 1.

Table 1: **Antibiogram of the methicillin-resistant *Staphylococcus aureus* strain with reduced susceptibility to glycopeptides**

Germe : Staphylococcus Aureus

Antibiotique	Interpretation
Céfoxitine	R
Gentamicine	S
Kanamycine	S
Lévofloxacine	S
Tobramycine	S
Oxacilline	R
Pénicilline G	R
Vancomycine	R
Teicoplanine	R

*R : resistant
*S : susceptible

-The determination of the minimum inhibitory concentrations (MICs) using the E-Test® strip method revealed resistance to both vancomycin and teicoplanin:

- **MIC for vancomycin**: 6 mg/ml
- **MIC for teicoplanin**: 8 mg/ml

The cytobacteriological examination of the hemodialysis catheter revealed the presence of methicillin-resistant *Staphylococcus aureus*, for which the antibiotic susceptibility results are presented in Table 2.

Table 2: **Antibiogram of the methicillin-resistant *Staphylococcus aureus* strain**

Germe : Staphylococcus Aureus

Antibiotique	Interpretation
Céfoxitine	R
Oxacilline	R
Erythromycine	S
Lincomycine	S
Pénicilline G	R
Kanamycine	S
Tobramycine	S
Gentamicine	S
Amoxicilline-Clavulanate	R
Céfotaxime	R
Amoxicilline	R
Ciprofloxacine	S
Norfloxacine	S
Lévofloxacine	S
Moxifloxacine	S

*R: resistant
*S: susceptible

A transthoracic echocardiography (TTE) was performed, and the results were normal. Following these findings, the patient was placed in contact and geographic isolation, with multi-drug resistant (MDR) organism signage placed on the patient's room door and in their medical file. The patient was started on linezolid

600 mg every 12 hours by intravenous infusion for 14 days, in combination with gentamicin, adjusted for renal function, for 4 days. The clinical course was marked by the regression of clinical signs, and follow-up blood cultures were all sterile.

It is noteworthy that the patient had never received prophylactic antibiotic therapy or prolonged treatment with vancomycin.

3. DISCUSSION

Different Strains of Vancomycin-Resistant *Staphylococcus Aureus* (VRSA):

True Vancomycin-Intermediate *Staphylococcus aureus* (VISA) was first reported in Japan in 1997, with the initial isolate obtained from a surgical wound of a 4-month-old infant who had undergone open-heart surgery (2). Two weeks post-surgery, the patient became febrile and developed a purulent discharge at the surgical incision site. Despite 29 days of vancomycin therapy, fever and drainage persisted. At this point, an aminoglycoside (arbekacin) was added to the vancomycin regimen for 12 days, resulting in wound healing and the discontinuation of antimicrobial treatment. However, 12 days later, the incision site became inflamed and an abscess developed. This was treated with a combination of arbekacin and ampicillin-sulbactam, and subcutaneous abscess debridement was performed. The debridement sample revealed a methicillin-resistant *Staphylococcus aureus* (MRSA) strain with a vancomycin MIC of 8 mg/L by broth microdilution. This represented the first clinical isolate of *S. aureus* demonstrating this level of vancomycin resistance, followed by reports of VISA emergence in other countries, including the United States, prompting efforts to limit its spread [2, 3].

To date, four VRSA isolates have been identified in the United States: two from Michigan, one from Pennsylvania, and one from New York [4]. The first clinical isolate was identified from a swab taken from the catheter exit site of a 40-year-old diabetic man from Michigan with peripheral vascular insufficiency and chronic renal failure [5]. Prior to this, the patient had been treated for chronic foot ulceration and had received several courses of antibiotics, including vancomycin. He developed MRSA after undergoing amputation of a gangrenous toe in April 2002, and was treated with vancomycin and rifampicin. A vancomycin-resistant *S. aureus* (VRSA) strain (MIC > 128 mg/L) and oxacillin-resistant *S. aureus* (MIC > 16 mg/L) were isolated from the drainage site, which appeared to heal a week after catheter removal, but the patient's chronic foot ulcer became infected. VRSA**,** vancomycin-resistant *Enterococcus faecalis*, and Klebsiella oxytoca were isolated from the ulcer. This strain exhibited high resistance to vancomycin (MIC > 128 mg/L by broth microdilution). Shortly after this report, another clinical VRSA isolate was described in Hershey, Pennsylvania, in September 2002, with a MIC of 32 mg/L [4]. This strain was isolated from a chronic foot ulcer in a 70-year-old morbidly obese hypertensive patient, who had received multiple courses of antibiotics (excluding vancomycin) in the past and presented with symptoms including lethargy, intermittent fever, chills, malaise, night sweats, and dyspnea on exertion for several weeks prior to presentation [4]. A third VRSA isolate was obtained from a urine culture and urinary catheter of a long-term hospitalized patient in New York in 2004 (MIC 32 mg/L) [6]. A fourth VRSA isolate was also reported in March 2005, the second identified in Michigan (2). The VRSA (MIC 256 mg/L) was isolated from a gangrenous toe wound of a 78-year-old man with a history of coronary artery disease, type 2 diabetes, peripheral vascular disease, neuropathy, chronic renal failure, and obstructive uropathy. Prior to the toe injury, the patient had been treated with vancomycin for most of the 9 weeks following an aortic valve replacement surgery. Although a vancomycin-susceptible Enterococcus faecalis isolate was recovered from the toe wound prior to amputation, a vancomycin-resistant E. faecalis isolate was recovered from a rectal surveillance culture from the same patient. Thus, vancomycin-resistant enterococci were isolated from three of the four VRSA patients, and in vivo transfer of the vanA gene may have occurred in this context. The pathogenesis of gene transfer in the Hershey patient remains unknown. A comparison of the first three of these VRSA strains with the strain from our patient is presented in Table 3.

Table 3: Comparison of Different Strains of Vancomycin-Resistant *Staphylococcus aureus* (VRSA).

		Souches VRSA		
Strains	**Michigan [a]**	**Hershey [b]**	**New York [c]**	**Our Case**
MIC for Voncomycin	1024 mg/L	32 mg/L	64 mg/L	6 mg/L
Previous Vancomycin Treatment	Yes	No	?	No
Vancomycin Resistant Enterococcus (VRE)	Yes	No	Yes[d]	No
Genetic Transfer	No	No	?	?
Asymptomatic Carrier	No	No	?	No

[a]Appelbaum et Bozdogan [7]
[b]Tenover *et al.*, [4]
[c]Kacica et McDonald [6].

Mechanisms of Vancomycin Resistance

Glycopeptides, such as vancomycin and teicoplanin, exert their antimicrobial effects by inhibiting the cell wall synthesis of *Staphylococcus aureus* [8]. It is currently believed that cell wall thickening and, potentially, the transfer of genetic material are the main mechanisms underlying vancomycin resistance. This resistance mechanism relies on the irreversible binding of vancomycin to the D-alanyl-D-alanine terminus of bacterial cell wall precursors, thereby blocking peptidoglycan assembly and inhibiting cell wall synthesis [2].

The resistance observed in *Vancomycin-Intermediate Staphylococcus aureus* (VISA) strains is thought to result from alterations in peptidoglycan biosynthesis. VISA strains synthesize an excess of peptidoglycan with increased amounts of D-alanyl-D-alanine residues, which bind to vancomycin molecules and effectively sequester them, preventing their bactericidal action (Figure 1) [2-9].

A recent study by Fox *et al*., [10], demonstrated that VISA strains are highly virulent in an experimental rabbit model of endocarditis. These strains have the potential to cause severe infections, emphasizing the need for rapid diagnosis and prompt treatment. Currently, no standardized treatment regimen exists for *VRSA* infections. However, all *VRSA* isolates have been found to be susceptible to several antimicrobial agents approved by the FDA. Moreover, an experimental endocarditis study using the first *VRSA* strain isolated in Michigan, along with an in vitro study using the *VRSA* strain from New York, suggests that therapy combining vancomycin with a beta-lactam antibiotic may be an effective option [10, 11].

It is important to highlight that surgical debridement and wound care are crucial treatment modalities for *VRSA* infections [12]. Other studies have suggested that high-dose daptomycin combined with another antibiotic, such as gentamicin, rifampicin, linezolid, trimethoprim-sulfamethoxazole (TMP-SMX), or a beta-lactam, is particularly effective against *VRSA*. Similarly, if reduced susceptibility to daptomycin is observed alongside vancomycin resistance, a combination or monotherapy with TMP-SMX, linezolid, or telavancin is recommended [1].

In our case, treatment with linezolid combined with gentamicin was highly effective, leading to a significant clinical improvement and sterilization of blood cultures.

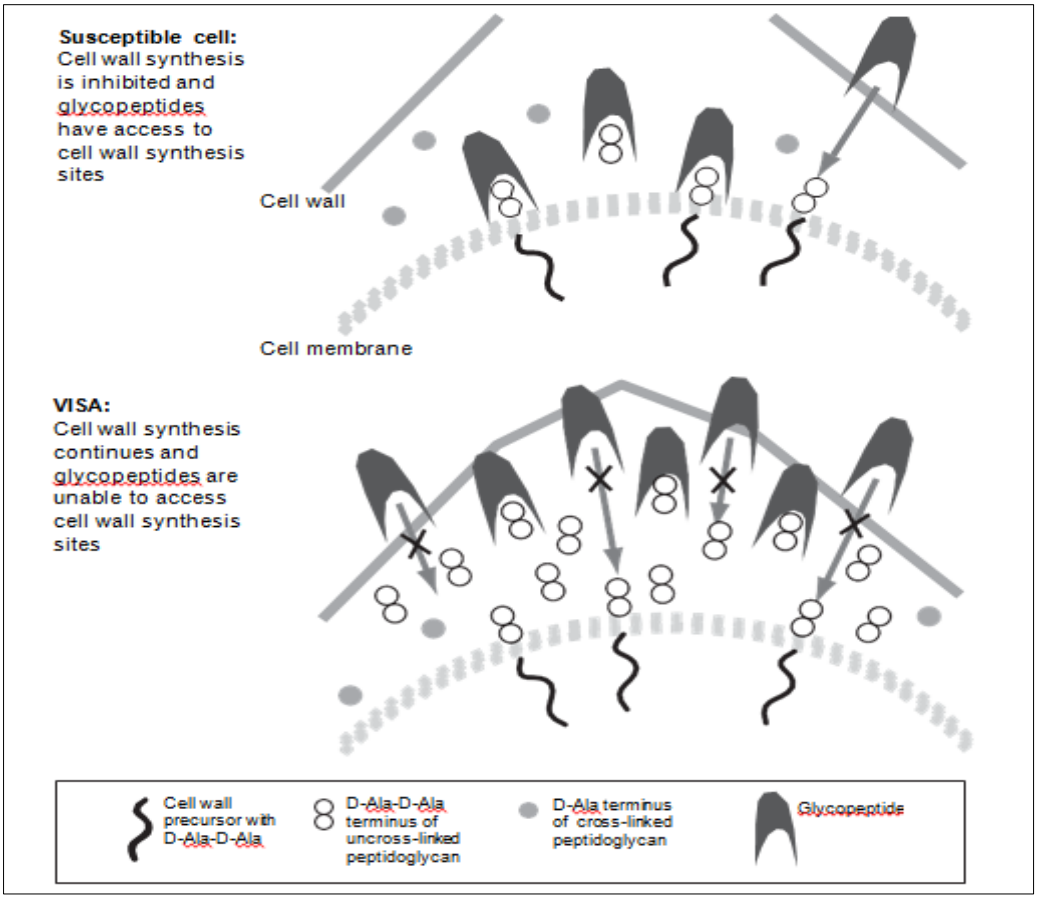

Figure 1: Cell wall thickening is a characteristic feature of VISA. Reproduced from Sieradzki *et al*., [24] with permission from The American Society for Biochemistry and Molecular Biology, Inc [2]

Minimum Inhibitory Concentration (MIC):

The vancomycin concentration required to inhibit most *S. aureus* strains generally ranges from 0.5 to 2 mg/L [13]. *S. aureus* isolates with vancomycin MICs of 8 to 16 mg/L are currently classified as vancomycin-intermediate, while isolates with MICs ≥ 32 mg/L are classified as vancomycin-resistant [13]. However, the Clinical and Laboratory Standards Institute (CLSI, formerly the National Committee for Clinical Laboratory Standards) has recommended that *S. aureus* isolates with vancomycin MICs of 4 mg/L should still be considered susceptible. In contrast, the Centers for Disease Control and Prevention (CDC) classifies these strains as potentially intermediate [13].

A key question remains whether systemic infections (e.g., endocarditis) caused by *S. aureus* strains with vancomycin MICs of 2 mg/L are truly clinically susceptible to vancomycin [14]. Some *S. aureus* strains with MICs of 4 mg/L, or even 2 mg/L, may not be truly susceptible in a clinical setting. Given this, it may be time for CLSI and CDC to reconsider lowering the recommended vancomycin screening concentration. In Europe, the French Society for Microbiology (SFM) and the Deutsches Institut für Normung (DIN) recommend screening plates with 6 mg/L of teicoplanin; however, this concentration is considered too high, and a teicoplanin concentration of 1–2 mg/L would be more appropriate. The VRSA isolate from Hershey, Pennsylvania, had a teicoplanin MIC of 4 mg/L, which is relatively close to that observed in our case, where the teicoplanin MIC was 8 mg/L [15].

Major Risk Factors:

One of the most critical unresolved questions is why five out of seven VRSA infection cases have occurred in Michigan. This regional emergence is likely due to a convergence of several factors, including population characteristics, antimicrobial pressure, and the presence of VRE strains more likely to donate the *vanA* operon. Michigan has a large population of individuals with underlying chronic illnesses, such as diabetes and end-stage renal disease, both of which appear to be associated with these infections. An estimated 590,000 adults (7.8% of the adult population) in Michigan have diabetes [16].

Diabetic patients frequently develop additional chronic conditions, including hypoesthesia in the feet, leading to unnoticed injuries (such as foot ulcers) from which VRSA has been isolated. Furthermore, diabetes is the leading cause of end-stage renal disease [17]. Dialysis patients are at high risk for invasive MRSA infections, leading to increased vancomycin exposure due to their reduced renal clearance, consequently resulting in prolonged exposure to subtherapeutic vancomycin levels. A recent report noted that the rate of invasive MRSA infection in dialysis patients is higher than in any other known patient population and is 100 times higher than in the general population [18]. This was also the case for our patient, who developed acute renal failure requiring hemodialysis, a significant risk factor for VRSA, particularly given the presence of a hemodialysis catheter as the presumed entry point.

In summary, VRSA infection remains a rare event. Several predisposing factors appear to contribute to VRSA infections, including prior MRSA or enterococcal infections or colonization, underlying conditions (such as chronic skin ulcers and diabetes), previous vancomycin treatment, and end-stage renal disease requiring hemodialysis. Further studies are needed to investigate the specific plasmid characteristics of *S. aureus* and VRE isolates from these patients. Appropriate antibiotic stewardship by clinicians, adherence to recommended infection control guidelines, and ultimately controlling MRSA and VRE are essential to preventing the emergence of new VRSA strains [12].

CONCLUSION

MRSA has spread from the community to a global scale. The increased use of vancomycin has led to selective pressure, triggering the emergence of VISA, followed by VRSA, raising alarms among physicians and microbiologists. Despite these concerns, VRSA infections remain rare.

Several specific factors appear to predispose patients to VRSA infections, including prior MRSA or enterococcal infections or colonization, underlying conditions (such as prolonged hospitalization, chronic skin ulcers, diabetes, and end-stage renal disease requiring hemodialysis), and previous vancomycin treatment. Targeted screening of high-risk patients is urgently required to assess the extent of VISA and VRSA infections, as well as vancomycin non-susceptibility in coagulase-negative staphylococci. Given the increasing antibiotic resistance, there is a clear need for the development of new classes of antibiotics with distinct mechanisms of action that remain effective against MRSA, VISA, and VRSA.

Funding: This research received no external funding.

Institutional Review Board Statement

The study was conducted in accordance with the Declaration of Helsinki, and approved by the Institutional Review Board of the Faculty of Medicine and Pharmacy FMPM, Cadi Ayyad University.

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement

The original contributions presented in the study are included in the article, further inquiries can be directed to the corresponding author.

Conflicts of Interest: The authors declare no conflict of interest.

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