A Patient with autoimmune hepatitis and transverse myelitis presented with persistent Staphylococcus aureus bacteremia, the discrepancies in assessing susceptibility; VISA versus Non-VISA

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Abstract
Vancomycin-Intermediate Staphylococcus aureus (VISA) is still uncommon among MRSA isolates. In our region, we rarely encounter a case of VISA and/or GISA bacteremia. Here, we report a man who suffered from autoimmune hepatitis on immunosuppressive therapy and thoracic transverse myelitis suspected to be due to polyomavirus infection; he developed persistent MRSA blood stream infection, PVL-positive and MLST clonal complex 88 which is reported most commonly from Africa. A strain with Vancomycin susceptibility of 4 – 6 µg/ml (VISA) was initially identified, retested again elsewhere and showed MIC of 2µg/ml and Teicoplanin susceptibility of 4µg/ml. Treatment failure occurred while attaining higher serum vancomycin levels than recommended and died.

Keywords: Vancomycin-intermediate S. aureus, VISA, S. aureus, Panton-Valentine-Leukocidin. Antimicrobial susceptibility testing
Introduction

Soon after the initial cases of Vancomycin-Intermediate *Staphylococcus aureus* (VISA) were reported from Japan in 1997, it relentlessly seems to be reported worldwide, predisposing for more vancomycin resistant strains i.e. VRSA, though it is still a rare sporadic isolate. However, VISA strains, a more frequent isolates compromise glycopeptides activity and complicate the treatment regimens of patients infected with these strains [1]. In an international study, *h*VISA phenotype (defined as the presence of subpopulations typically at a rate of 1 organism per $10^5$–$10^6$ of MRSA with VISA) occurred in more than one-quarter of MRSA blood isolates from patients with infective endocarditis, though it varied in frequency by geographic region [2, 3]. In Taiwan, isolates from ten centers collected 1000 MRSA, the prevalence of VISA isolates were 0.2% and *h*VISA isolates 0.7% [4].

In our region, reports from the Arab Countries have been published; In Jordan a case of VISA (MIC = 4 mg/dl) was reported in the year 2006 by F. Bakri and coworkers in a patient with erythrodermic psoriasis who suffered three months persistent *Staphylococcus aureus* bacteremia [5]. MRSA strains with decreased susceptibility for vancomycin were reported from Qassim region in Saudi Arabia [6]. VISA, *h*VISA persistent blood stream infection in spite of high blood vancomycin levels were reported from Saudi Arabia as well [7]. Another interesting report came from Oman on the treatment of infective endocarditis due to VISA; a patient was treated with a combination of intravenous linezolid and fusidic acid without a need for surgical intervention and resulted in complete cure [8]. Moreover, a report on glycopeptide-intermediate *Staphylococcus aureus* (GISA) were reported from north Lebanon, five strains out of 113 (4.4%) were resistant to teicoplanin (GISA) by MIC dilution method and no strain was resistant to vancomycin. Although all MRSA isolates were reported as susceptible by Muller-Hinton agar diffusion method [9], we should consider other methods for testing MRSA for MIC when it is needed.

Here, we present a patient who was immuno-suppressed and had had suffered from persistent *Staphylococcus aureus* blood stream infection in spite of being on unintentional high serum levels of vancomycin. The isolate show discrepant susceptibility testing between different laboratories, once was interpreted as VISA, at another institution was not.

Case Report

A 47 year old male patient from Yemen with type 2 diabetes mellitus on insulin, and autoimmune hepatitis since 1996 on Immunosuppressive therapy; dexamethasone 4 mg/day and azathioprine 50 mg twice daily. He was admitted on November 1, 2014 in Jordan hospital complaining of bilateral lower limb weakness of one month duration, it was sudden in onset and progressive, it was noticed when lifting heavy objects, and later falling down spontaneously on walking. Dorsal spine MRI imaging showed lesion in the anterior part of dorsal spine (Figure 1). Differential diagnosis included viral transverse myeli-
tis, demyelination, and low grade neoplasm.

He was transferred from another hospital with decreased level of consciousness; he was admitted to the ICU, and on admission he was sleepy, generally weak and could not move his legs. CSF analysis showed WBC = 44/mm$^3$, RBC = 100/mm$^3$, Protein = 308 mg/dl, Glucose = 148 mg/dl, he was started on ceftriaxone 2gm/12 hours and vancomycin 1gm/12 hours. Dorsal MRI showed a lesion of the anterior part of the spinal cord, extending opposite the lower part of D5 to the lower part of the D6 vertebral bodies, it showed no significant enhancement in the post contrast images (Figure 1). Dexamethasone was discontinued on November 3rd and methylprednisolone 1gm/24 hours was started. On November 6th he started fever (38.6°C orally) when an infectious diseases consultation was sought. Laboratory tests for Clostridium difficile toxins, CMV IgM, toxoplasma IgM, urine legionella antigen, mycoplasma IgM, and Chlamydia pneumoniae IgM, HIV antibodies, HCV Antibodies and HBsAg were all negative. Urine sediment for decoy cells was positive, and BK-Polyomavirus by Taq-Man real time PCR (Anatolia Genework Inc, Istanbul, Turkey) was positive. Immunosuppressive therapy was advised to be tapered and ceftriaxone and vancomycin were discontinued as aerobic blood cultures twice showed no growth with abating fever. Few days later he redeveloped fever, and blood culture grew Enterobacter cloacae, he was started on piperacillin/tazobactam 4.5 gm/8 hours, fever subsided for several days and the patient was relatively stable with his baseline neuro-deficit. A repeat dorsal spine MRI showed no significant changes from previous imaging and no evidence of new lesions.

About a week later, the patient developed high fever (38.4°C), and his blood cultures grew methicillin-resistant Staphylococcus aureus (MRSA), vancomycin 2gm IV loading followed by 1gm/12 hours was started, 2D- echocardiogram was normal, and bone scan was reported as multiple abnormal areas of increased radiotracer uptake seen at both sterno-clavicular joints, both knee joints, and irregular tracer uptake is seen at D5-D6 and D12 vertebral bodies.

Five days into vancomycin treatment; on November 19th fever persisted, and empiric fluconazole 600mg IV loading then 400mg IV/24 hours was added, vancomycin trough levels were monitored aiming to keep levels 15 - 20 µg/ml, although in most instances levels were unintentionally elevated due to measured deterioration in renal function (Figure 3). The patient did not have clinical response, vancomycin E-test (bioMérieux Marcy l’Etoile. 376, chemin de l’Orme 69280 Marcy l’Etoile) was done and initially showed complete resistance (CLSI MIC > 16 µg/ml), an immediate repeat of the E-test resulted in vancomycin-intermediate Staphylococcus aureus (VISA) MIC = 4 – 6 µg/ml (CLSI MIC for VISA equals 4 – 8 µg/ml) (Figure 2). Linezolid 600 mg IV/12 hours and imipenem/cilastatin 250 mg/6 hours were started; the latter and fluconazole were discontinued as repeat blood cultures showed the same S. aureus isolate. The patient showed continuous clinical de-
terioration, white lungs on chest radiogram, poor arterial blood gases, electrolytes imbalance, further renal function deterioration, intractable shock and met his demise.

**MIC and Molecular analysis**

Due to E-testing discrepancy at our laboratory, a preserved *Staphylococcus aureus* isolate was retested for susceptibility by the (Antimicrobial Resistance and Healthcare-Associated Infections Reference Unit. Public Health England, 61 Colindale Avenue, London NW9 5EQ, Reference number PHE ref. No.: H1 5020 1048), and showed that vancomycin MIC was 2 µg/ml (CLSI vancomycin susceptible ≤ 2), while teicoplanin MIC was 4 µg/ml (CLSI susceptible ≤ 8). *Staphylococcus aureus* typing revealed spa type: t690, (repeat succession: 07-12-21-17-13-34-34-33-34) and Panton-Valentine-Leukocidin (Luk-PV) positive strain.

**Discussion**

In our region, we rarely document patients with MRSA-induced sepsis with elevated or creeping MIC phenomena, and persistent bacteremia while on vancomycin treatment, due to resources limitations. A case was presented by my group (Rula Rashed MD, Fadi Shaqlous PharmD) earlier in 2010, in a regional meeting; the isolate demonstrated creeping vancomycin MIC [10] while the patient was on treatment with therapeutic vancomycin levels, MIC creped in a month time from 0.125 µg/ml, to 0.75 µg/ml, to 1.5 µg/ml as was verified by E-test. The patient continued to have pus discharge from a traumatized combat-related infected foot wound with repeated surgical debridement, till he was switched to linezolid with almost brisk response and discharged home (unpublished report).

Our current patient was immunocompromised, and had thoracic spinal cord transverse myelitis that was suspected to be due polyomavirus infection, which may have been predisposed by immunosuppressive therapy. Again he showed lack of response to vancomycin therapy, though the strain was within the susceptibility range, and vancomycin serum levels were much higher than what was desired (Figure 3). Failure of vancomycin therapy for VISA strains is well described, as the target attainment (AUC/MIC ≥ 400) cannot be reached [11]. Higher failure rates were also reported with “creped” vancomycin MIC, though still within susceptibility ranges of ≤ 2 µg/ml; the upper CLSI limit for vancomycin susceptibility [12, 13]. Our *S. aureus* isolate as retested in (Antimicrobial Resistance and Healthcare-Associated Infections Reference Unit. Public Health England, 61 Colindale Avenue, London NW9 5EQ), it exhibited vancomycin susceptibility and did not meet CLSI MIC level for GISA [12,14].The isolate belongs to spa type that has been associated with PVL-MRSA and belonging to MLST clonal complex 88 reported most commonly from Africa. This mecA positive *S. aureus* encodes Pantone-Valentine leuocidin (PVL) genes. Infection with PVL-SA most commonly presents as primary cutaneous lesions [15, 16]. However PVL-positive *S. aureus* was reported to be associated with serious life threatening disease, namely community-associated pneumonia (CAP) in four patients, all did not have the classical risk factors for infection with strains carrying PVL genes [17].The patient was started on Linezolid but the duration of therapy was not enough to appreciate a response, and he died.

In our case, a lesson to be learned; laboratories should pay attention for microorganisms’ antimicrobial susceptibility testing, taking into account the imported tests kits source, storage and quality; here the E-tests strips that showed discrepant MIC values for *S. aureus* in the same laboratory and tests strips brand, though labeled as not expired; E-test (bioMérieux Marcy l’Etoile. 376, chemin de l’Orme 69280 Marcy l’Etoile).
Another lesson learned from this case, that a persistent fever in compromised patients is a risk factor for the development of more antibiotic resistant patterns of S. aureus infections and moreover in PVL-positive strains. This study also suggests the early implementation of antibiotic treatment based on suspicion of the frank pathogen, in order to cover strains with higher MICs, before the actual MIC is available [18].

Acknowledgement

We thank Professor David Livermore for his cooperation, and we thank Doctor Robert Hill for his assistance (Head of Antibiotic Susceptibility. Antimicrobial Resistance and Healthcare-Associated Infections Reference Unit. Public Health England, 61 Colindale Avenue, London NW9 5EQ)

References

1. Hiramatsu K, Aritaka N, Hanaki H, Kawasaki S, Hosoda Y, et al. Dissemination in Japanese hospitals of strains of Staphylococcus aureus heterogeneously resistant to vancomycin. Lancet. 1997;350(9092):1670-3
2. In-Gyu Bae, Jerome J. Federspiel, Jose´ M. Miro´, Christopher W. Woods, Vance G. Fowler Jr et al. Heterogeneous Vancomycin-Intermediate Susceptibility Phenotype in Bloodstream Methicillin-Resistant Staphylococcus aureus Isolates from an International Cohort of Patients with Infective Endocarditis: Prevalence, Genotype, and Clinical Significance. Jour Infect Dis 2009; 200:1355–66
3. Tenover FC, Moellering RC Jr. The rationale for revising the Clinical and Laboratory Standards Institute vancomycin minimal inhibitory concentration interpretive criteria for Staphylococcus aureus. Clin Infect Dis 2007; 44:1208–15
4. Ho CM, Hsueh PR, Liu CY, Lee SY, Chiueh TS, et al. Prevalence and accessory gene regulator (agr) analysis of vancomycin-intermediate Staphylococcus aureus among methicillin-resistant isolates in Taiwan--SMART program, 2003. Eur J ClinMicrobiol Infect Dis 2010,29(4):383-9. doi: 10.1007/s10096-009-0868-4
5. Faris G. Bakri, Nisreen Abu AL-Hommos, AemShehabi, Randa G. Naffa, Longzhu Cui et al. Persistent bacteraemia due to
methicillin-resistant Staphylococcus aureus with reduced susceptibility to vancomycin in a patient with erythrodermic psoriasis. Scandinavian Journal of Infectious Diseases 2007;39(5):457-460.

6. Abdulateef A. Alzolibani, Ahmad A. Al Robaee, Hani A. Al Shobailal, Jalal Al Bilal, Mohammad Issa Ahmad et al. Documentation of vancomycin-resistant Staphylococcus aureus (VRSA) among children with atopic dermatitis in the Qassim region, Saudi Arabia. ActaDermatovenerologicaAlpina, Pannonica et Adriatica 2012;21:51-53. doi:10.2478/v10162-012-0015-2

7. S. Al-Obeid, Q. Haddad, A. Cherkaoui, J. Schrenzel, and P. Francois. First Detection of an Invasive Staphylococcus aureus Strain (D958) with Reduced Susceptibility to Glycopeptides in Saudi Arabia. J Clin Micro 2010; 48(6): 2199–2204. doi:10.1128/JCM.00954-09

8. Abdullah Bakhair, Zakariya Al Muhrami, Laila Darwish, Hatem Farhan, Mansour Sallam. Treatment of vancomycin-intermediate Staphylococcus aureus (VISA) endocarditis with linezolid; Case Report. International Jour Infect Dis 145 (2010) e227–e229. doi:10.1016/j.ijid.2009.07.023

9. El Ayoubi M-D, M. Hamze, H. Mallata, M. Achkar, F. Dabboussi. Glycopeptide intermediate Staphylococcus aureus and prevalence of the luk-PV gene in clinical isolates, in Northern Lebanon. Med Mal Infect (2014), http://dx.doi.org/10.1016/j.medmal.2014.03.004

10. Gregory Steinklaus, Roger White and Lawrence Friedrich. Vancomycin MIC creep in non-vancomycin-intermediate Staphylococcus aureus (VISA), vancomycin-susceptible clinical methicillin-resistant S. aureus (MRSA) blood isolates from 2001–05. J AntimicrobChemother 2007; 60:788–794

11. Natasha E. Holmesa, John D. Turnidgec, Wendy J. Munckhofe, J. Owen Robinson, Tony M. Kormanh, et al. Vancomycin AUC/MIC Ratio and 30-Day Mortality in Patients with Staphylococcus aureus Bacteremia. Antimicrob. Agents Chemother. 2013;57(4): 1654-1663

12. Glycopeptides Susceptibility. Performance Standards for Antimicrobial Susceptibility Testing; Twenty-fifth International Supplement. CLSI January 2015. M100-S25

13. Ravina Kullar, Susan L. Davis, Donald P. Levine, and Michael J. Rybak. Impact of Vancomycin Exposure on Outcomes in Patients With Methicillin-Resistant Staphylococcus aureus Bacteremia: Support for Consensus Guidelines Suggested Targets. Clin Infect Dis. 2011;52(8): 975-981

14. SweSwe-Han K, Naidoo N, Mahabeer P, Milisana K. First detected isolate of glycopeptide-intermediate resistant Staphylococcus aureus in a renal unit at a central academic hospital in KwaZulu-Natal. South Afr J Epidemiol Infect 2013;28(2):126-129

15. Matthew J. Ellington, Mark Ganner, Marina Warner, Barry D. Cookson, and Angela M. Kearns. Polyclonal multiply antibiotic-resistant methicillin-resistant Staphylococcus aureus with Panton–Valentine leucocidin in England. Journal of Antimicrobial Chemotherapy. doi:10.1093/jac/dkp386

16. M. J. Ellington, C. Perry, M. Ganner, M. Warner, I. McCormick Smith, R. L. Hill et al. Clinical and molecular epidemiology of ciprofloxacin-susceptible MRSA encoding PVL in England and Wales. Euro Jour Clin Micro Inf Dis 2009;28(9):1113-1121

17. John S. Francis, Meg C. Lopatin, Cecilia P. Johnston, Gita Sinha, Tracy Ross. Severe Community-Onset Pneumonia in Healthy Adults Caused by Methicillin-Resistant Staphylococcus aureus Carrying the Panton-Valentine Leukocidin Genes. Clin Infect Dis. (2005);40 (1): 100-107.doi: 10.1086/427148

18. Scott K. Fridkin. Vancomycin-Intermediate and –Resistant Staphylococcus aureus: What the Infectious Disease Specialist Needs to Know. ClinInfecDis 2001; 32:108–15.

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