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INFECTIOUS DISEASES | RESEARCH ARTICLE

Vancomycin-resistant *Staphylococcus aureus* isolates among hospitalized patients; a tertiary medical care center experience from Southern Iran

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Abstract: Background and Objective: Bacterial resistance to different types of antibiotics has been globally emerging over recent years. The present study was carried out to investigate the rate of vancomycin-resistant *Staphylococcus aureus* (VRSA) at a tertiary medical care center in Kerman, Iran. **Materials and Methods:** In this cross-sectional study, 250 samples with positive culture for coagulase-positive *S. aureus*, taken from the suspected infectious sites of patients admitted to different medical and surgical wards at Bahonar hospital from 2009 to 2011, were studied. **Results:** 9.2% of *S. aureus* isolates were found to be vancomycin-resistant. There was no significant difference in the rate of resistance between males and females (8 vs. 12.9%, respectively). Though the rate of resistance was shown to be marginally higher in post-surgical compared to medical ward patients, the difference was statistically insignificant ($p = 0.8$). Across the wards, general surgery housed the largest number of patients with VRSA (20%). **Conclusion:** The emergence of VRSA isolates has perhaps not received a great deal of attention so far. It appears that the increasing use of vancomycin in non-complicated infections may contribute to the emergence of *S. aureus* isolates which turn to be vancomycin-resistant.

Subjects: General Medicine; Infectious Diseases; Medicine

Keywords: *Staphylococcus aureus*; vancomycin; bacterial resistance; Iran

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Farhad Sarrafzadeh is an assistant professor at Kerman University of Medical Sciences with clinical practice in the field of Infectious Diseases and Tropical Medicine at Kerman Medical University affiliated hospitals. One of the main interests pursued in his academic endeavors is the Antimicrobial Stewardship Program. The goal of the program is to ascertain optimal antibiotic therapy in patients afflicted with infections. In line with the above, a clear understanding about antibiotic resistance patterns is expected to guide optimized clinical approaches particularly when a specific antimicrobial agent is being used. His present study was an attempt to identify the rate of vancomycin-resistant *S. aureus* (VRSA) at a tertiary medical care center in Kerman, Iran. The stewardship program will continue to assess the rate of resistance in other centers at provincial and geographical scales through which future directions toward optimal treatments against VRSA and other resistant strains will be defined.

PUBLIC INTEREST STATEMENT

Today, resistance to antimicrobial treatment is a serious issue, leading to a rapid spread of various organisms for which few treatments are available. Antimicrobial Stewardship refers to coordinated interventions designed to improve and measure the appropriate use of antimicrobials by promoting the selection of the optimal antimicrobial drug regimen, dose, duration of therapy, and the route of administration. The major objectives of antimicrobial stewardship are to achieve optimal clinical outcomes related to antimicrobial use, to minimize toxicity and other adverse events, and to limit the selection for antimicrobial resistant strains. Antimicrobial stewardship may also reduce excessive costs attributable to suboptimal antimicrobial use. To this end, one major step is to define the resistance pattern for a specific organism when certain antibiotic is being used in large scale. This study was done to assess the rate of vancomycin-resistant *Staphylococcus aureus* isolates among hospitalized patients in our setting.

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1. Introduction

Staphylococcus aureus is a common culprit in nosocomial including blood stream, and surgical site infections as well as pneumonia, and continues to be a major pathogen in community-acquired infections worldwide (Brooks, Carroll, Butel, Morse, & Mietzner, 2010). In acute and severe infections, *S. aureus* is among the most common pathogens isolated from skin, eyes, cerebrospinal fluid, blood, respiratory and gastrointestinal tract, bone, and connective tissues. When disseminated, *S. aureus*-related infections such as bacteremia may enhance the mortality rate up to 40% (Brooks et al., 2010; Fauci, Longo, & Hauser, 2012). Immune-deficient patients, those who underwent surgery, and very young or very old patients are considered as high risk for *S. aureus* infection (Katzung, 2007, 2009). Since over the half of *S. aureus* isolates are known to be resistant to methicillin, the glycopeptide vancomycin has been widely used as one of first proper alternative choices for the treatment of methicillin-resistant *S. aureus* (MRSA) (Katzung, 2009).

The clinical isolates of vancomycin-intermediate *S. aureus* (VISA), typically represent a thicker cell wall when grown in glycopeptides (Mandell, Bennett, & Dolin, 2010). Studies have documented that due to an increasing resistance to methicillin, physicians tend to use vancomycin quite widely (Katzung, 2007, 2009; Palazzo, Araujo, & Darini, 2005). The first recognized type of *S. aureus* which demonstrated decreased sensitivity to vancomycin was reported in 1997 and only few years later, vancomycin-resistant *S. aureus* (VRSA) isolates were introduced (Palazzo et al., 2005). The use of wide-spectrum antibiotics, especially vancomycin is increasing at many tertiary medical care centers and referral hospitals worldwide. Research in the field of antibiotic resistance is expected to provide helpful insights on the susceptibility and transmission route of infections, identifying the etiologic factors, and practical measures to decrease morbidity and mortality rates in hospitalized patients. Moreover, careful analysis of such findings may help in determining pathogens' sensitivity and ultimately lead to optimized infection control policies at any hospital.

In clinical practice, normally the first step towards proper utilization of antibiotics is to start with broad-spectrum antibiotics depending upon suspected source and organisms followed by rapid de-escalation of the therapy once the organism is identified and minimum inhibitory concentration (MIC) is available to prevent emergence of MDRO (multidrug-resistant organisms). Despite the above practice, the emergence of new resistant strains may put forward ongoing challenges in antibiotic therapy.

The recently witnessed lack of expected response to vancomycin (potentially owing to VRSA) prompted us to evaluate the possible emergence of VRSA isolates among hospitalized patients in Bahonar hospital (a tertiary medical care center) in Southern Iran.

2. Materials and methods

In this cross-sectional study, samples were obtained from hospitalized patients in Bahonar hospital, Kerman, Iran over two years (2009–2011). Patients were informed about the investigation and signed written consents accordingly. All included patients were febrile and clinically suspected to have active infection. Patients were admitted to various medical and surgical wards including orthopedics, general surgery, neurosurgery, endocrinology, hematology, and intensive care unit (ICU). Most patients ($n = 210$) were already operated in their current hospitalizations. Post-operative patients were admitted to the ICU, general surgery, neurosurgery, and orthopedics wards. Specimens were obtained from suspected sites for infection (including blood, sputum, urine, cerebral spinal fluid (CSF), synovial fluid, and wounds) and were instantly transferred to the laboratory for investigations. The collected specimen types comprised blood, wound exudates, urine, CSF, sputum, and synovial fluid. Respiratory tract secretions were obtained through bronchoalveolar lavage or deep suction with sterile Nelaton catheter in patients who were intubated. Urinary tract samples were taken using the sterile method (clean catch mid-stream or supra-pubic puncture).

To take specimen from the wound, wounds were first washed and samples were collected using sterile cotton swabs. For blood cultures, assuming that the number of micro-organism colonies could vary in different time points, two separate blood specimens were taken 15 h apart. Using the

sterile method, CSF samples were mainly obtained in post-surgery patients with indwelled shants or ventriculostomy catheters. In some patients however, samples were collected through lumbar puncture. In all cases, 5–10 ml CSF was taken in three test tubes for culture, staining, and cytology.

With regard to laboratory evaluations, briefly, all retrieved specimens were cultured in blood agar media and samples which were positive for *Staphylococcus* were evaluated in coagulase slide test. *Staphylococcus* specimens which were found positive in coagulase slide test were considered *S. aureus.* To confirm the diagnosis, culture in mannitol salt agar media and DNase test were performed. Specimens confirmed to be culture positive for *S. aureus*, were submitted for antibiogram.

Epsilometer test (*E*-test) strips for vancomycin (Biomerieux, Sweden) and disk diffusion method were used for antibiogram. Having the *S. aureus* specimens cultured in Mueller Hinton agar media, we could concurrently measure the disc inhibition zone and MIC. This protocol allowed *E*-test and disk diffusion at the same time. MIC was used to determine *S. aureus* resistance to vancomycin. Agar plate was inoculated and vancomycin diffused from a disk or from a paper strip into the agar. The growth inhibition zone and MIC were measured the next day. According to the breakpoints of Clinical and Laboratory Standards Institute (Sabra & Abdel-Fattah, 2012), MIC < 2 was considered as sensitive, 4 < MIC < 8 as semi-sensitive, and MIC > 16 as resistant.

Statistical analysis was done using the SPSS-15 software. Chi-square, or Fisher's exact test were employed to compare nominal variables. *p* values less than 0.05 were considered as significant.

3. Results

In this study, a total of 250 samples which were found positive for *S. aureus* were examined for possible resistance to vancomycin. One hundred and eighty-eight samples (75.2%) were obtained from male patients and 62 (24.8%) from females. Table 1, demonstrates the rate of resistance with regard to gender, age, as well as the type of surgery. Fifteen (8%) and 8 (12.9%) specimens from male and female patients, respectively, were found to be resistant to vancomycin. As shown in Table 1, surgery did significantly affect vancomycin resistance in male and female patients (*p* = 0.04).

Patients were classified into three groups based on their age (younger than 18, 19–64, and up to 65 years) with the highest rate of resistance documented in the 19–64 year-old age group (*n* = 194). Meanwhile, the difference in resistance rate among various age groups was statistically insignificant (*p* = 0.5).

Table 2 demonstrates the rate of *S. aureus* resistance to vancomycin based on the admission wards. The highest rate of resistance (20%) was recorded in general surgery ward, while the number of samples was quite low (*n* = 5). The statistical analysis did not show a significant difference amongst different wards with regard to the rate of resistance (*p* = 0.6).

Table 1. Comparison of vancomycin-resistant *S. aureus* isolates based on age, gender, and surgery during the same hospitalization

Resistance	Background						
	Sex (%)		Surgery (%)		Age by years (%)		
	Male	Female	Operated	Non-operated	18	19–64	65
Sensitive and semi sensitive	173	54	190	37	28	173	26
	(92)	(87.1)	(90.5)	(92.5)	(96.5)	(89.2)	(96.3)
Resistant	15	8	20	3	1	21	1
	(8)	(12.9)	(9.5)	(7.5)	(3.5)	(10.8)	(3.7)
Total	188	62	210	40	29	194	27
	(75.2)	(24.8)	(84)	(16)			
p value	0.2		0.04		0.5		

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Table 2. Vancomycin-resistant *S. aureus* isolates in different wards to which patients were admitted							
	Wards						
Resistance	**Orthopedics**	**ICU**	**ER**	**Endocrinology**	**Hematology**	**Neurosurgery**	**General surgery**
Sensitive and semi sensitive	128	21	1	27	11	35	4
	(92.8)	(87.5)	(100)	(96.4)	(84.6)	(85.4)	(80)
Resistant	10	3	0	1	2	6	1
	(7.2)	(12.5)	(0)	(3.6)	(15.4)	(14.6)	(20)
Total	138	24	1	28	13	41	5
	(55.2)	(9.6)	(0.4)	(11.2)	(5.2)	(16.4)	(2)

Notes: ICU: Intensive Care Unit, ER: Emergency Room.

All *S. aureus*-infected specimens were further classified into six groups based on their source. The sampling sources were urine, CSF, blood, sputum, wound, and synovial fluid. Although most specimens were taken from wounds ($n = 74$), the majority of resistant isolates were seen in CSF samples ($n = 14$, resistance rate = 28.6%). Further analysis revealed no significant difference between vancomycin resistance and the sampling site ($p = 0.2$). Based on the culture and sensitivities in our laboratory, VISA and VRSA strains were found to be sensitive to co-trimoxazole, daptomycin, tigecyclin, and linezolid.

Putting these into perspective, it appears that the frequent and often not necessarily rationale use of antibiotics as well as the presence of complicated nosocomial infections at a center which has long been known as tertiary and referral, have predominantly resulted in the emergence of such a resistance. To ensure continued surveillance on the antibiotic resistance patterns, our registry is still ongoing. We plan to continue recording annual data to support antibiotic stewardship program at our center.

4. Discussion

S. aureus is known to be a significant hospital and community-associated pathogen causing a wide range of infectious diseases (Centers for Disease Control & Prevention, 2014). In the Middle East region, some studies with contradictory results have attempted to define the rate of antimicrobial resistance in hospitalized patients (El-Jakee et al., 2011; Sabra & Abdel-Fattah, 2012; Sarafzadeh, Sohrevardi, Gharehghozli, & Ahmadinejad, 2010).

Since the prevalence of resistance to various antibiotics has steadily increased, the selection of an effective antimicrobial agent against coagulase-positive staphylococcus like *S. aureus* remains a challenge (Brooks et al., 2010). One study from Pakistan which investigated the antibiotic resistance pattern in clinical isolates of *S. aureus*, reported only one isolate as vancomycin-resistant (Kaleem et al., 2012). We however found 23 out of 250 *S. aureus* isolates (9.2%) to be vancomycin-resistant (Table 2). Such a significant disparity in results might have resulted from several contributors including the regional difference in infection control and antibiotic use policies.

Following a systematic literature search using the keywords methicillin-resistant *S. aureus* and VRSA, a total of 88 reports were retrieved. A systematic review of all available resources suggested an increasing rate of Vancomycin Intermediate *S. aureus* (VISA) and VRSA emergence worldwide (Taj, Abdullah, & Kazmi, 2010). In an analysis by Hawser et al. and other similar reports, the MICs of vancomycin were considerably high in all methicillin-sensitive *S. aureus* (MSSA) and methicillin-resistant *S. aureus* (MRSA) from 2004 to 2009 (Hawser, Bouchillon, Hoban, Dowzicky, & Babinchak, 2011; Loomba, Taneja, & Mishra, 2010; Tiwari & Sen, 2006).

In the current investigation, we studied 250 samples from different wards at Bahonar hospital-Kerman, a tertiary medical care and trauma center. The majority of samples were obtained from wounds since most patients were admitted to orthopedic, neurosurgery, and general surgery ward mainly due to trauma.

In this study, the emergence of vancomycin resistance was studied in patients whose specimens were found positive for *S. aureus*. Patients' data were analyzed in subgroups based on gender, age, operative status, wards, and the site of specimen. Despite the predominance of male patients (*n* = 188), the rate of resistance was higher in females. There was no significant difference with regard to the history of operation during current hospitalization and the rate of resistance. Most of the patients were operated (*n* = 210). Among operated subjects, only 9.5% demonstrated resistance. Non-operated patients were mainly admitted to medical wards including endocrinology and hematology and comprised a relatively few number (*n* = 40). The analysis did not demonstrate any significant correlation between surgery and the rate of resistance. Most *S. aureus* specimens with vancomycin resistance were obtained from 19 to 64 year-old patients. Our study revealed no significant correlation between the age and rate of resistance. Most surgical patients were admitted to the orthopedics ward mainly due to motor vehicle accident. While the rate of resistance amongst orthopedic patients was 7.2%, patients admitted to the general surgery ward (*n* = 5) demonstrated the resistance rate of 20%. According to our analysis, no statistically significant correlation between wards and resistance rate was noted. Although the majority of specimens were obtained from surgical wounds, the highest rate of resistance was observed in the CSF samples of patient who underwent neurosurgery (28.6%). This might have possibly resulted from the type of procedure, sensitivity of the organ, and the involved pathogen strains.

In an Indian study, Tiwari et al. reported VISA/VRSA in and in and around the investigation area. They found 2 out of 783 *S. aureus* strains as vancomycin- and teicoplanin-resistant. In addition, six strains were found to be of vancomycin intermediate sensitivity using the MIC method (Tiwari & Sen, 2006).

In the same vein, two other studies from India revealed some strains of VISA as well as the emergence of hVRSA (heteroVRSA) strains showing heterogeneous resistance to vancomycin (Assadullah et al., 2003; Tiwari & Sen, 2006). Based on the cumulating evidence on vancomycin-resistant *S. aureus*, VRSA appears to be a major concern for clinicians both in tertiary and community medical care centers in many centers. In line with what we found, the increasing resistance to various antibiotics in developing countries seems to be associated with the irrational use of antibiotics. Easy access to antibiotics even without prescription leads to indiscreet use either at hospital or outpatient setting (Song et al., 2000). The presence of VISA/VRSA may therefore be potentially linked to the wide use of vancomycin.

Vancomycin-included combination therapies may be deemed effective in the treatment of *S. aureus* and its resistant strains ubiquitously found in nosocomial and community-acquired infections. Treatment of VRSA is challenging and these isolates are shown to be multidrug-resistant against many available antibiotics. This makes the treatment options limited, and consequently the inadequate antibiotic therapy may lead to an increased morbidity and mortality in afflicted cases (Kaleem et al., 2012).

Though current practice guidelines suggest the use of combination therapy in empirical regimens for patients with difficult to treat infections, evidence from well-designed randomized trials is lacking. Ideally, empirical regimens for life-threatening infections should cover all likely pathogens. If this is not possible by giving one drug, combination therapy can be used, however this needs to be streamlined to specific monotherapy as soon as the microbiology reports are available (Ahmed, Azim, Gurjar, & Baronia, 2014).

The combination of doripenem or imipenem + vancomycin (Kobayashi, 2005; de Lassence et al., 2006), doripenem + teicoplanin (de Lassence et al., 2006), and imipenem + linezolid (Miranda-Novales, Leaños-Miranda, Vilchis-Pérez, & Solórzano-Santos, 2006) are shown to be appropriately covering MRSA. However, imipenem + teicoplanin is among the very few combinations with proven evidence to cover VRSA (Jacqueline et al., 2005).

Ertapenem is a carbapenem with no activity against MRSA. The use of such narrower spectrum carbapenem when the infection is not complicated and MRSA is not suspected may be proper step toward antibiotic stewardship and the prevention of resistance (Gesser, McCarroll, & Woods, 2004; Jacqueline et al., 2005, 2006).

The seemingly rapid emergence of vancomycin resistance requires an urgent control. This can be done at least partly through educating health care professionals on nosocomial infections, infection control policies, and the wise use of antibiotics.

5. Conclusion

This study provided initial evidence on the rate of resistance to vancomycin in clinical isolates of *S. aureus* from a tertiary medical care center in Southern Iran. A relatively high rate of resistance in *S. aureus* (9.2%) raises a warning flag about a challenging antibiotic resistance in our setting. There was no significant correlation between the rate of resistance and age, gender, surgery, or sampling site. Understanding the local susceptibility patterns is crucial to treatment optimization.

Together with other referral hospitals in our province and hopefully through fostering multi-centric collaborations towards antibiotic stewardship at national scale, we need to take instant initiatives against antibiotic resistance in our practice. This is not only expected to facilitate the outbreak detection and prevention innovation, but also to improve antibiotic use and reduce antibiotic resistance.

Establishing and promoting multi-centric collaborations through public–private partnerships based on the insights from research and development in the field of antibacterial therapy is the key step towards antibiotic stewardship. This would incentivize development of new therapeutics to counter antibiotic resistance, including new, next-generation, and other alternatives to antibiotics, vaccines, and affordable, rapidly deployable, point-of-need diagnostics. Overall, strategies need to be materialized to prevent and control the emergence and spread of antibiotic resistance through evidence-based interventions.

We recommend utilizing such antibiotic resistance study results towards a defined antibiotic stewardship program at national and regional levels.

Competing interests
The authors declare no conflict of interest.

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