

Prospective Study of Irrational Prescription of Teicoplanin in a Large Academic Hospital: A Dilemma of Antimicrobial Resistance

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INTRODUCTION

Methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant enterococci (VRE) are among the most important microorganisms responsible for nosocomial infections.^[1] Currently, increase in the number of MRSA and VRE infections complicates the treatment and increase the disease burden.^[2,3]

It seems that the minimum inhibitory concentration (MIC) of glycopeptides against MRSA strains is increasing worldwide.^[4,5] Increasing MIC, even by small amounts, correlates with treatment failure; therefore, MIC data are necessary to optimize antimicrobial therapy in the clinical setting.^[5]

ABSTRACT **Objective:** Teicoplanin is an antibiotic used to treat severe Gram-positive infections, especially those caused by methicillin-resistant *Staphylococcus aureus* (MRSA). In this study, we aimed to evaluate the pattern of teicoplanin rational prescribing to identify the factors which affected rational utilization. In addition, the teicoplanin minimum inhibitory concentration (MIC) was assessed in randomly selected isolates. **Methods:** In this descriptive-analytical prospective study, a total of 256 patients were randomly selected to evaluate the pattern of teicoplanin use. The required data were gathered to assess the appropriateness of teicoplanin usage. Also, 100 teicoplanin Etests were used for measuring the MIC. **Findings:** The results showed that the appropriateness rate of teicoplanin usage was 21.9%. The mean MIC was 2.24 ± 5.47 mg/L for the MRSA cultures (33 cultures), including 32 sensitive cultures (97%). In addition, the mean MIC was 28.71 ± 8.29 mg/L for the vancomycin-resistant enterococci (VRE) cultures (67 cultures), including five sensitive cultures (7.5%). Moreover, the analysis revealed that only the hospitalization ward was statistically significantly related to irrational usage ($P = 0.014$). **Conclusion:** The high prevalence of the inappropriate use of teicoplanin will lead to the development of antimicrobial resistance. Furthermore, the high rate of VRE cultures resistant to teicoplanin proves that teicoplanin has no advantage over vancomycin for treating VRE infections. Finally, we recommend guidelines' development for the appropriate administration of teicoplanin.

KEYWORDS: Drug utilization review, Methicillin-resistant *Staphylococcus aureus*, microbial sensitivity test, Teicoplanin, Vancomycin-resistant enterococci

Medication use evaluation (MUE) studies aligned with MIC measurement could be helpful in promoting infection control.^[6,7] Despite the importance of the rational use of antibiotics, frequent irrational prescribing is a common problem, especially in developing countries.^[8,9]

Irrational usage of teicoplanin for many years caused the increase of MRSA species resistant to glycopeptides,

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which necessitates an evaluation of its use.^[4,10-12] According to the surveys conducted so far, there has not been any study evaluating teicoplanin consumption patterns, specifically in the Middle East. Therefore, because of the importance of this issue, the study was designed not only to assess the teicoplanin consumption pattern but also to identify risk factors associated with the irrational administration of that. Also, we aimed to evaluate the teicoplanin MIC in MRSA and VRE isolates.

METHODS

This descriptive-analytical and prospective study was carried out at Al-Zahra Hospital, the largest referral tertiary academic hospital located at the center of Iran (Isfahan), for 12 months from August 2017 to 2018.

In the current study, 256 patients were randomly selected from all patients who received at least one dose of teicoplanin based on hospital pharmacy information and followed daily until teicoplanin was discontinued or the patient died.

To evaluate the rational usage of teicoplanin, the medication administration information, laboratory findings, microbiological culture results, and antibiogram (if samples were sent to the laboratory) were recorded. We also gathered the vital sign data to assess the systemic inflammatory response syndrome (SIRS) criteria. Moreover, any possible adverse drug reactions related to teicoplanin were reported.

We used four indicators to evaluate SIRS criteria, including temperature, heart rate, respiratory rate, and white blood cell. If two or more of these indicators were observed in the patient, the SIRS criteria would be positive.^[13]

Teicoplanin prescriptions were categorized into three groups: prevention, empirical, or targeted. The prophylactic use of antibiotics occurs before or after surgery to reduce the chances of infection.^[14] Empirical treatment is selected based on the severity of patients' condition, history of previous antibiotic administration and culture results, local antibiotic resistance, and the clinical judgment of physicians.^[14] In the targeted antimicrobial therapy, the administration is based on the culture results and the antibiogram that is reported from the laboratory.^[14]

The standard dose of teicoplanin for mild-to-moderate infections is 6 mg/kg body weight (400 mg in adults) every 12 h for three administrations and continued every 24 h. The dose for severe infections is 12 mg/kg (800 mg in adults) with the same intervals.^[15]

Usage appropriateness was evaluated based on treatment protocols, obtained from the guidelines and reliable

resources of infectious diseases, including Mandell *et al.*,^[14] Sanford,^[16] and the electronic Medicines Compendium.^[15] Finally, different aspects of teicoplanin appropriate use were evaluated in this study [Table 1]. When all the leading indicators (including indication after 72 h, dosage, and treatment duration) were appropriate, we considered the usage appropriate, which was reported at the end of the patients' follow-up.

To evaluate the microbial resistance to teicoplanin, 100 isolates were randomly selected from the current patients' microbiological cultures. The Etest is a reliable technique to assess the susceptibility of *S. aureus* to teicoplanin.^[17] It is worth noting that the susceptibility of the isolates was assessed based upon the Clinical and Laboratory Standards Institute.^[18]

Sensitive = MIC \leq 8 mg/L, intermediate = 8 mg/L < MIC < 32 mg/L, resistant = MIC \geq 32 mg/L.

At first, the collected data were entered into the SPSS 23 (SPSS Inc., Chicago, IL, USA). One proportion of the Z-test was conducted to evaluate if more than 80% of patients followed the scientific standards for teicoplanin administrations' parameters. Pearson's Chi-square test was used to find an association between 2 categorical variables in the population. Also, logistic regression was performed to evaluate the association of demographic and baseline clinical factors with misuse of teicoplanin.

The patient's extracted information will be kept confidential. This research was accepted by Isfahan University of Medical Sciences' ethical committee (research ID = 193107).

RESULTS

During 1 year, 256 patients were assessed and teicoplanin utilization was surveyed. The mean age of the patients was 54.85 ± 18.84 years and 62.1% of cases were male. The interval between hospital admission and beginning teicoplanin administration was an average of 7.69 ± 12.67 days. The mean duration of the administration was 12.75 ± 8.89 days. It should be noted that 76.2% of patients had a history of broad-spectrum antibiotic treatment in the previous 4 weeks.

In the 98.4% of cases, an infectious diseases specialist prescribed teicoplanin or an infectious disease consult was done at the beginning of the treatment. The SIRS criteria of more than 80% of patients were positive at the beginning of the study. The cultures were requested for 95.3% of patients at the start of teicoplanin treatment [Table 2 for information about the culture results].

The most antibiotics prescribed concurrently with teicoplanin were beta-lactam plus beta-lactamase inhibitors (including ampicillin/sulbactam and

Table 1: The standards for evaluating the appropriateness of indication, dosage, treatment duration and usage

Subject	Indicators
Appropriate indication after 24 h	Rational reason of administration AND rational reason why teicoplanin was preferred to vancomycin (acute or chronic renal failure, history of adverse reactions of vancomycin, co-administration of other nephrotoxic medications such as furosemide and aminoglycosides, any other risk of nephrotoxicity)
Appropriate indication after 72 h	Appropriate indication after 24 h AND rational reason to continue teicoplanin administration (sensitive culture results at the initiation of treatment, previous history of sensitive culture results, positive SIRS criteria*)
Appropriate dosage	Appropriate loading and maintenance dosage according to the indication, weight and renal dose adjustment (If required)
Appropriate treatment duration	Should be decided based on the clinical response For infective endocarditis and osteomyelitis, a minimum of 21 days is usually considered appropriate. Treatment should not exceed 4 months
Appropriate usage	When appropriate indication after 72 h, dosage and treatment duration we accomplished

*Positive SIRS criteria increases the risk of septic shock. Hence, continue antimicrobial therapy is almost rational when the SIRS criteria is positive. SIRS=Systemic inflammatory response syndrome

Table 2: Characteristics of Teicoplanin administration and microbial culture results

Characteristics	Total (n=256), n (%)
Unit	
ICU	55 (21.5)
Medical wards	166 (64.8)
Surgical wards	35 (13.7)
Indication type	
Prophylactic	15 (5.9)
Empirical therapy	240 (93.8)
Targeted therapy	1 (0.4)
Culture result at the initiation of teicoplanin	
Not requested	12 (4.7)
No growth of bacteria after 72 h	56 (21.9)
MRSA	42 (16.4)
MSSA	6 (2.3)
VRE	69 (27)
Other Gram-positive bacteria [‡]	14 (5.5)
Gram-negative bacteria	48 (18.8)
Fungi	4 (1.6)

[‡]Except MRSA, MSSA and VRE. Categorical variables are expressed as, n (%). MRSA=Methicillin-resistant *Staphylococcus aureus*, MSSA=Methicillin-sensitive *Staphylococcus aureus*, VRE=Vancomycin-resistant enterococci, ICU=Intensive care unit

piperacillin/tazobactam) (52.7%) and carbapenems (30.1%).

The appropriate indication rates were 96.5% and 53.5% in the first 24 h and after 72 h, respectively. Additionally,

78.1% of the dosage regimens and 57.4% of treatment duration were suitable. Finally, the appropriateness of teicoplanin usage was calculated as 21.9%.

One proportion of Z-test showed indication after 72 h, and the duration and usage of teicoplanin were significantly inappropriate ($P < 0.001$).

Different variables were evaluated to find factors that could predict the misuse of teicoplanin by the univariate analysis [Table 3]. Accordingly, age, hospitalized ward, indication for prescription, the reason for administration and infectious specialist consultation were significantly associated with misuse of teicoplanin. However, when multivariate regression was developed, only patients who received teicoplanin in intensive care units had significantly lower misuse of teicoplanin ($P = 0.014$, odds ratio = 0.179, 95% confidence interval = 0.43–0.734) [Table 3].

In the context of possible adverse reactions to teicoplanin, three cases of decreased platelet count and two cases of red neck syndrome were reported.

As mentioned in the methods section, 100 teicoplanin Etests were provided (Liofilchem®, Italy) and randomly used for the microbiological cultures that had MRSA or VRE. The mean MIC for MRSA (33 cultures) was 2.24 ± 5.47 mg/L, including 32 sensitive (97%) and one resistant (3%) cultures. The mean MIC for VRE (67 cultures) was 28.71 ± 8.29 mg/L, including 5 sensitive (7.5%), 57 intermediate (85.1%) and 5 resistant (7.5%) cultures.

DISCUSSION

In this study, the irrational prescription of teicoplanin is relatively high. There is not a specific, large study to evaluate its administration. The only related study was conducted in postcoronary artery bypass grafting patients in 2016, which demonstrated teicoplanin as the most inappropriate prescribing antibiotic compared with meropenem, imipenem, and linezolid.^[19] In this study, the appropriate use of teicoplanin was reported 34.48% in 26 patients that is higher than 21.9% reported in our study among 256 patients.^[19] Study design, clinical setting and time of the study, in addition to variation in the definition of the appropriate teicoplanin usage, could explain the reasons for different results between our research and previously conducted studies. We evaluated the appropriateness of teicoplanin usage after 72 h and identified the misuse based on the indication, culture results, rational choice, dosage and treatment duration. However, in the mentioned study, the errors of teicoplanin administration were only reported based on the dosage and/or treatment duration.

Table 3: Variables associated with misuse of Teicoplanin

Variables	Analysis				
	Univariate regression		Multivariate regression		
	P	OR	P	OR	95% CI
Age ≤60 years	<0.001	3.839	0.639	1.173	0.603-2.281
Hospitalization ward	<0.001		0.044		
Intensive care	<0.001	2.667	0.014	0.179	0.43-0.734
Medical	<0.001	3.743	0.124	0.396	0.115-1.362
Surgical*	-	-	-	-	-
Indication for prescription	<0.001		0.367		
Skin and soft tissue infections	<0.001	2.774	0.791	1.413	0.192-10.383
Bone and joint infections	0.998	>109	0.998	>108	
Pneumonia	<0.001	4.556	0.267	3.530	0.416-29.972
Urinary tract infections	<0.001	6.800	0.197	4.502	0.488-41.532
Prophylaxis (before surgery)	0.206	0.500	-	-	
Bacteremia	0.999	109	0.999	109	
Endocarditis	0.999	109	0.999	>108	
Intra-abdominal infection*	-	-	-	-	
Reason of administration	<0.001		0.302		
Antibiotic prophylaxis	0.206	0.500	0.485	0.618	0.160-2.384
Empirical therapy	<0.001	4.217	0.248	3.778	0.396-36.075
Targeted therapy*	-	-	-	-	
Infectious specialist consultation	<0.001	3.500	0.80	0.700	0.04-12.221

*Reference group. OR=Odds ratio, CI=Confidence interval

A decrease of 43% in the appropriate indication rate after 72 h in comparison with 24 h was observed in our study, which is compatible with results of the previous MUE study of vancomycin.^[20] This decline is in accordance with the culture results reported after 72 h. More than 70% of culture results did not sensitive to teicoplanin, but in most cases, it had not been discontinued. Paying no attention to the laboratory reports of microbial cultures, severe condition of clinical condition and uncertainty about the accuracy of laboratory results may be the most important reasons for the continuation of teicoplanin, despite negative culture results. Therefore, we suggested a more prolonged evaluation (at least 72 h) for MUE of antibiotics.

We found administration of teicoplanin more appropriate in intensive care wards than medical or surgical wards. Perhaps, the critical condition of these patients attracted more attention from a specialist, or because of the high prevalence rate of resistant microorganisms in these wards, administration of teicoplanin was considered appropriate based on clinical judgment of a physician, even when culture is negative in empiric therapy.

However, the resistant MRSA to teicoplanin is not a new threat, but our results showed the incremental trend of resistant MRSA to teicoplanin compared with previous studies conducted in Iran.^[21,22] Even if all MRSA strains were sensitive, and increased MIC for MRSA (especially in concentrations of more than 1.5–2 mg/L

for teicoplanin) informs the reduced susceptibility in MRSA.^[23,24] In recent years, frequent and unrestricted use of glycopeptides resulted in increased MIC for MRSA and subsequently, treatment failure.^[21,25] It is a signal to stop the unreasonable prescribing of antibiotics.

In regard of co-administered antibiotics, beta-lactam plus beta-lactamase inhibitors and carbapenems composed more than 80% of them. As these antibiotics have broad-spectrum activity on hospital-acquired Gram-negative bacilli, their combination with glycopeptides rendered the best choice for the treatment of more than 90% of our population who received empirical therapy.

We observed a few adverse effects of teicoplanin through all 256 patients. Generally, teicoplanin has lower side effects than vancomycin.^[26] The prevalence of nephrotoxicity and drug sensitivity reaction in the patients treated with vancomycin is higher than teicoplanin.^[27] Moreover, thrombocytopenia is one of the unusual but important undesirable effects of teicoplanin.^[15,16]

In accordance with previous surveys, cross-resistance to VRE between vancomycin and teicoplanin also exists in the present study.^[3,28] Therefore, vancomycin is the preferable option than teicoplanin due to less therapeutic cost until there is a risk of nephrotoxicity or previous history of vancomycin adverse effects.^[27]

This prospective study gives not only valuable information about the pattern of teicoplanin administration, but also introduces the possible factors which predict inappropriate use of teicoplanin and propose strategies to reduce improper usage of teicoplanin. It also gives warning about the gradual increase in the rate of resistant MRSA to teicoplanin. However, this study was performed in a regional academic hospital over a year which may limit our results.

However, therapeutic drug monitoring (TDM) is recommended to adjust teicoplanin therapy in literature, but because of the high cost and required equipment, it did not perform routinely mainly in developing countries.^[29]

However, there was no protocol for regulating antibiotic therapy and re-evaluating it after 72 h in our setting at the time of the study, but fortunately, it is now prepared and implemented by the antimicrobial stewardship committee of our hospital.

Codification of hospital guideline and be committed to it, frequent consultations to infectious disease specialist, more active cooperation and legal intervention of clinical pharmacist in patients' treatment, implementation the automatic stop and start program in hospital information system (HIS) to control automatically stopping and restarting the antibiotic and continuous application of educational program, maybe efficacious in maintaining and improving the appropriate use antimicrobial agents, over time.

The emergence of resistant MRSA is progressively increased especially in developing countries, which necessitate applying intervention accordingly.

We suggest an automatic stop order of antibiotics, clinical pharmacist consultation, and clinical guidelines development and implementation for the appropriate administration of teicoplanin and other vital antibiotics for infectious diseases. Moreover, TDM is recommended to achieve therapeutic plasma level and prevent sub-optimal concentrations, which cause emergence of resistant microorganisms and eventually treatment failure.

AUTHORS' CONTRIBUTION

Shadi Farsaei and Kiana Shirani provided the concept and the idea of the research, Masoud Hajjaligol gathered the data, Shadi Farsaei and Masoud Hajjaligol analyzed the data and prepared the drafted manuscript. All authors contributed in revising the final version and approved it for submission.

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Conflicts of interest

There are no conflicts of interest.

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