



Does AUC/MIC Ratio Predict Efficacy and Safety of Vancomycin?

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Abstract

In this review, the studies in which potential correlation between the area under the curve/minimum inhibitory concentration ratio of vancomycin (AUC/MIC) and its efficacy and safety had been considered, were assessed. Papers that had defined the potential correlation between vancomycin AUC/MIC and its efficacy, safety, or both as a primary outcome were included. Considering that extent of vancomycin exposure as well as susceptibility of microorganisms were both included, AUC/MIC seemed to be a more accurate index than serum trough concentration for predicting vancomycin efficacy. However, data regarding correlation between this index and vancomycin-induced nephrotoxicity are limited. Different breakpoints have been defined for AUC/MIC. The optimized use of vancomycin can improve its efficacy and defer the occurrence of tolerance. Further studies are needed to define optimum vancomycin AUC/MIC breakpoints and in turn predict its efficacy and safety.

Keywords: Vancomycin, AUC/MIC, Efficacy, Safety

Background

Gram-positive microorganisms including *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Enterococcus faecium*, and *Enterococcus faecalis* are recognized as common causes of nosocomial infections (1-2). About 45.6% of episodes of severe sepsis are due to Gram-positive organisms, among which, *Staphylococcus aureus* is involved in 62.7% of occasions (1).

Following the advent of resistant microorganisms, limited options are available for the treatment of infections due to the presence of methicillin resistant *S. aureus* (MRSA) (3,4). However, despite the introduction of newer agents for the treatment of MRSA infections, vancomycin remains still the gold standard of treatment (4-7).

Adverse effects of vancomycin including red man syndrome, nephrotoxicity, ototoxicity, local phlebitis, hypersensitivity reactions, neutropenia, and thrombocytopenia are the infusion related, concentration-dependent, or idiosyncratic reactions (5-9).

To assess the efficacy and safety of vancomycin, therapeutic drug monitoring (TDM) has been recommended (7,10). Moreover, serum trough level and AUC/MIC are introduced as pharmacokinetic (PK) and pharmacokinetic/pharmacodynamic (PK/PD) surrogate markers of vancomycin monitoring. Although AUC/MIC is more accurate, due to less sampling, vancomycin trough level is more practical (10). In this respect, serum trough levels of vancomycin between 10-15 mg/L and 15-

20 mg/L are recommended for the treatment of mild to moderate and serious infections, respectively (7, 10).

The correlation between serum trough level of vancomycin and its efficacy and safety has been evaluated. However, few data are available regarding the correlation between efficacy and safety of vancomycin and AUC/MIC index (11-13).

Hence, the studies that had considered the potential correlation between vancomycin AUC/MIC and its efficacy and safety were assessed in this review.

Methods

To extract data, biomedical databases including Scopus, Medline, and Google Scholar were considered. The applied keywords were 'vancomycin', 'efficacy', 'safety', and 'AUC/MIC'.

Papers that defined potential correlation between vancomycin AUC/MIC and its efficacy, safety, or both as the primary outcome were included. Time for resolving the signs and symptoms of infection, stabilization of hemodynamic parameters, clearance of inflammatory biomarkers, microbial eradication, and patient's survival were defined as vancomycin efficacy. Additionally, incidence of vancomycin-induced nephrotoxicity (VIN) and ototoxicity were considered for evaluating the safety of vancomycin. Non-English language articles and case reports were excluded.

Results

In a preliminary screening, 61 articles, as well as 20 articles from these were found and included in this study. Correlation between vancomycin AUC/MIC and its efficacy, safety, or both were evaluated in 13, 4, and 3 articles, respectively (Figure 1). Studies are summarized in Table 1.

Studies that Evaluated Correlation Between Vancomycin AUC/MIC and Efficacy

In a retrospective study by Brown et al, correlation between vancomycin AUC/MIC and infection-related mortality was evaluated in 50 patients with complicated bacteremia (32 patients) or infective endocarditis (18 patients). According to the Classification and Regression Tree (CART) analysis, AUC_{24h}/MIC breakpoint equal to 211 was associated with infection-related mortality. Thirteen patients (26%) had AUC_{24h}/MIC <211 and 37(74%) patients had AUC_{24h}/MIC ≥211. The mean total daily dose of vancomycin was 22 mg/kg/d in patients with AUC_{24h}/MIC ≥211 and 16 mg/kg/d in those with AUC/MIC <211. The medium duration of treatment was 11 days in the AUC_{24h}/MIC≥211 group compared to 18 days in the AUC_{24h}/MIC <211 group. In addition, MIC was measured by E-test method in this study. All-cause and infection-related mortality rates were 24% and 16%, respectively. The infection-related mortality in the patients with AUC_{24h}/MIC <211 was approximately 5 times more than that in the patients with AUC_{24h}/MIC ≥211 (38% versus 8% respectively). All-cause mortality was also higher in the AUC_{24h}/MIC <211 group compared to the AUC_{24h}/MIC≥211 group (46% versus 16% respectively) (14).

In a cohort study, association between patient's mortality and first 96-hour AUC/MIC value was evaluated. This

study included 182 patients with *S. aureus* bacteremia. Primary outcome was 30-day mortality and secondary outcomes were persistent positive blood culture (≥7 days after the first culture) and reappearance of bacteremia within 30 days. MIC was determined with both broth microdilution (BMD) and E-test methods in this study. The mean values of MIC were 1 mg/L in BMD method and 1.5 mg/L in E-test method. Breakpoints of AUC/MIC in BMD and E-test methods were 373 and 226, respectively. Both breakpoints were estimated by the CART analysis. The probable rate of survival for patients with AUC/MIC ≤373 was lower than that for those who had AUC/MIC >373 (71.6% versus 84.3% respectively). Patients who reached AUC/MIC >373 had 12% lower mortality rate than those who did not reach this value. In this study, early achievement to AUC/MIC ≥400 during the treatment course of *S. aureus* bacteremia correlated with better survival rate. However, this association was not significant. Additionally, type of microorganism and patient's characteristics were significantly correlated with survival (15).

In another study by Ghosh et al, 127 patients with bloodstream infections due to *S. aureus* were included. In this study, sources of infections were divided into low (intravenous catheter, urinary tract, ear-nose-larynx, and gynaecological source), intermediate (osteo-articular sources, soft tissue, and unknown sources), and high risk (endovascular sources, pneumonia, abdominal sources, and central nervous system foci) groups. Primary outcome was treatment failure. Treatment failure was defined as overall 30-day mortality, persistent bacteremia (≥7 days), microbiological failure, or persistent signs of infection up to 14 days after beginning the treatment. Out of 127 patients, 45 (35.4%) had the treatment failure criteria, out of which, 11 (24%) had persistent bacteremia, 12 (26%)

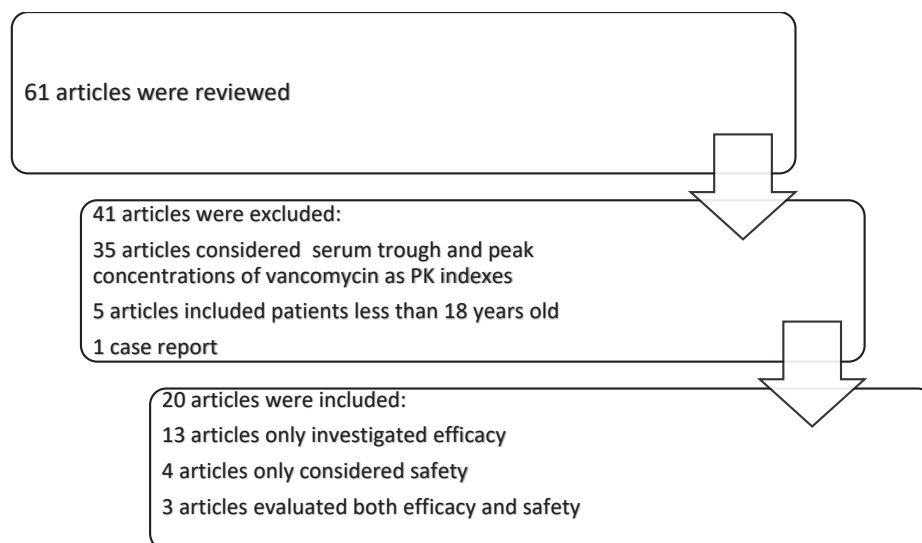


Figure 1. Flowchart of Study.

Table 1. Summary of Studies on Correlation Between Vancomycin AUC/MIC and its Efficacy and Safety

Year of publication	Author (s)	No. of included patients	Type of infection	Goals	Defined break point (AUC/MIC or AUC)	Outcome	Conclusion	Strengths of study	Weaknesses of study
2009	Lodise et al	166	Different infections	Correlation between extent of exposure to vancomycin and incidence of VIN	1300 (AUC)	VIN	Patients with AUC values ≥ 1300 experienced more VIN	Assessment of different aspects of VIN	Single center, Retrospective
2011	Kullar et al	320	Bacteremia	Association between vancomycin exposure and outcomes	421	Treatment failure and VIN	Outcome improved in patients with AUC/MIC >421 , but incidence of VIN increased	Assessment of MIC	Retrospective study, Multiple initial site of infection
2012	Brown et al	50	Bacteremia and Infective endocarditis	Relationship between AUC/MIC and mortality	211	Mortality	Infection-related mortality was lower in patients with AUC/MIC values ≥ 211	Both efficacy and safety aspects were considered	Small sample size, Retrospective, Single center
2012	Suzuki et al	31	Pneumonia	Correlation between PK-pharmacodynamic parameters and safety and efficacy of vancomycin	629.1 \pm 272.8	Response to treatment and VIN	Trough level of vancomycin was sufficient for TDM of vancomycin	Both efficacy and safety aspects were considered	Small sample size, Retrospective
2012	Zelenitsky et al	35	Septic shock	Defining optimal AUC/MIC in patients with septic shock	578	Mortality	In patients with septic shock, target AUC/MIC of 578 was defined	Defined new breakpoint for AUC/MIC in septic shock	Retrospective, Small sample size
2012	Suzuki et al	31	Pneumonia	Assessing VIN according to different PK parameters	540.6 (AUC)	VIN	AUC and Cmin but not Cmax were equally useful in predicting VIN	Cosidering different PK variables	Small sample size, Retrospective
2013	Holmes et al.	182	Bacteremia	Correlation between AUC/MIC and mortality	373 ^a , 226 ^b	30-day mortality	Mortality was more related to the properties of microorganisms and host factors than to vancomycin AUC/MIC	Assessment of MIC with two methods	Including various bacterial strains
2013	Gawronski et al.	59	Bacteremia and osteomyelitis	Association between vancomycin AUC ₂₄ /MIC and time to microbial clearance and VIN	293	Microbial clearance time and incidence of VIN	Patients with AUC/MIC >293 had faster microbial clearance	Evaluation of both e efficacy and safety of vancomycin	Retrospective, Small sample size
2013	Mizokami et al.	94	Hospital-acquired pneumonia	Relationship between 28-day mortality and extent of exposure to vancomycin	250-450	28-day mortality	AUC breakpoint goal between 250-450 was recommended for pneumonia treatment	Considering specific infection and population, evaluating both efficacy and safety of vancomycin, considering severity of disease	Retrospective, Small sample size
2013	Ampe et al.	20	Different infections	Correlation between AUC/MIC and treatment failure in patients receiving continuous infusion of vancomycin	667 ^c , 451 ^d	Treatment failure	Patients who achieved the target AUC/MIC, had fewer treatment failure	Defining AUC/MIC breakpoints for both free and total serum levels of vancomycin, assessing both safety and efficacy of vancomycin	Including different types of infections

Table 1. Continued

Year of publication	Author (s)	No. of included patients	Type of infection	Goals	Defined break point (AUC/MIC or AUC)	Outcome	Conclusion	Strengths of study	Weaknesses of study
2013	Mizokami et al	94	Pneumonia	Correlation between vancomycin PK parameters and 28-day mortality	AUC = 250-450	VIN	In AUC greater than 450, incidence of VIN increased	Patients had comparable demographic data (age)	Small sample size, Retrospective, AUC values were not adjusted according to MIC values
2014	Ghosh et al	127	Bacteremia	Defining optimal vancomycin AUC0-24/MIC target in patients with MRSA bacteremia	398 ^a , 270 ^b	Treatment failure	Successful treatment in patients with AUC/MIC more than the breakpoint	Assessment of MIC with 2 methods, Defined AUC/MIC targets for bacteremia based on the sources	Retrospective
2014	Jung et al	76	Bacteremia	Association between AUC/MIC of vancomycin and treatment failure	398.5 ^a , 430 ^b	Treatment failure	Improvement of outcome in patients with AUC/MIC>400	Assessment of MIC with two methods, considering patient's specific parameters	Heterogeneity of sources of infection
2014	Lodise et al	123	Bacteremia	Correlation between extent of exposure to vancomycin and the patients' outcome	521 ^e , 650 ^f 303 ^g , 320 ^h	Treatment failure	Patients who achieved target AUC/MIC, had fewer treatment failure	Evaluating both efficacy and safety of vancomycin	Retrospective
2015	Casapao et al	139	Infective endocarditis	Correlation between vancomycin exposure on day 1 of treatment and treatment failure	AUC0-24h/ MICBMD = 600	Treatment failure	AUC / MIC ≤600 increased treatment failure	Assessment of MIC with two methods, evaluation of both efficacy and safety of vancomycin	Retrospective, Small sample size
2016	Britt et al	53	Bacteremia	Considering AUC/MBC and AUC/MIC values of vancomycin as predictors for mortality	AUC/MIC: 334-400 AUC/MBC: 176	30-day mortality	AUC24h/MIC(BMD) ≥ 334-400 improved survival, AUC/MBC was a better predictor of mortality than AUC/MIC	Defining new breakpoint of AUC/MBC for 30-day mortality	Retrospective, Small sample size
2016	Fukumori et al	81	Hospital-acquired pneumonia	Assessment of response to vancomycin based on AUTL index	AUTL = 331	Response to vancomycin and incidence of VIN	Vancomycin AUTL showed stronger association with its efficacy compared to AUC24h	Defining a new index; AUTL for monitoring the vancomycin	Population but not patients' specific data were considered
2017	Martirosov et al	71	Bacteremia	Correlation between extent of exposure to vancomycin and treatment failure	AUC24-48h = 550, AUC/MIC = 336	Treatment failure	Patients who achieved target AUC, had fewer treatment failure	Measuring MIC with both Etest and BMD methods	Retrospective, Small sample size

Table 1. Continued

Year of publication	Author (s)	No. of included patients	Type of infection	Goals	Defined break point (AUC/MIC or AUC)	Outcome	Conclusion	Strengths of study	Weaknesses of study
2017	Hale et al.	100	Different sites of infection	Correlation between serum trough concentrations of vancomycin and the achievement of AUC/MIC \geq 400	400	Correlation between serum trough level and target and AUC/MIC of vancomycin, Incidence of VIN as a secondary outcome	Reaching vancomycin serum trough level of 15-20 mg/L relative to the trough level of 10-14.9 mg/L did not increase the likelihood of reaching the target AUC/MIC	Evaluating safety and efficacy of vancomycin according to both trough and AUC/MIC indexes	Retrospective, Small sample size
2017	Frinch et al.	1280	Different infections	AUC-Guided Vancomycin Dosing and VIN	AUC = 471.5	VIN	Vancomycin dosing according to AUC was associated with lower VIN	Partially large sample size	Retrospective, Efficacy was not considered
2017	Zasowski	323	Bacteremia and pneumonia	Association between initial vancomycin AUC and incidence of VIN	AUC _{0-48h} = 1218 AUC _{0-24h} = 677 AUC _{24-48h} = 683	VIN	Daily AUC of vancomycin between 600-800 mg.h/L increased risk of NIN 3 to 4 times	Defining 3 thresholds for AUC based on the times of treatment	Single center, retrospective, efficacy was not considered
2017	Chavada et al	127	Bacteremia	Relationship between VIN and AUC _{0-24h}	AUC = 563	VIN	Incidence of VIN in patients with AUC $>$ 563 was more than that in patients with AUC $<$ 563	Defining breakpoint of AUC for VIN	Retrospective, efficacy was not considered
2017	Hale et al	100	Different sites of infection	Correlation between different vancomycin PK parameters (trough serum concentration and achievement of AUC/MIC \geq 400) and VIN	400	VIN	Patients with higher trough level experienced more VIN	Evaluating both efficacy and safety	Retrospective, small sample size

^aAUC/MIC from BMD method.

^bAUC/MIC from E-test method.

^cAUC/MIC in free portion level group.

^dAUC/MIC in total serum level group.

^eAUC/MIC from BMD method (first 24 h).

^fAUC/MIC from BMD method (second 24 h).

^gAUC/MIC from E-test method (first 24 h).

^hAUC/MIC from E-test method (second 24 h).

VIN: Vancomycin-induced nephrotoxicity; AULT, Area under trough vancomycin.

had microbiological failure, and 22 (48%) died. Seven (15%) patients had more than one criterion for treatment failure. In this study, MIC values were measured with two methods of E-test and BMD, with average values of 2 mg/L and 1 mg/L, respectively. AUC/MIC (BMD) breakpoints for low, intermediate, and high-risk sources of infections were 330, 363, and 440, respectively. According to the CART analysis, overall breakpoint of AUC/MIC (BMD) was determined as 398. Fifty (39%) patients had AUC/MIC <398, out of which, 27 (54%) patients experienced treatment failure. On the other hand, among patients with AUC/MIC \geq 398 (77 patients), 18 (23.4%) had treatment failure. The similar results were detected according to AUC/MIC (E-test), but breakpoint value for this method was 270. In the low-risk group, 15 out of 38 (39.5%) patients had AUC/MIC <330 and 23 (60.5%) had AUC/MIC \geq 330. Treatment failure was observed in 2 out of 23 (8.7%) and 6 out of 15 (40%) patients with AUC/MIC values \geq 330 and <330, respectively. In the intermediate-risk group, 17 out of 50 (34%) and 33 out of 50 (66%) patients had AUC/MIC values <363 and \geq 363, respectively. Among patients with AUC/MIC <363, 7 out of 17 (41%), and in group with AUC/MIC \geq 363, 4 out of 33 patients (12%) experienced treatment failure. In the high-risk group, 19 out of 39 (48.7%) patients had AUC/MIC <440, and 20 (51.3%) had AUC/MIC \geq 440. Treatment failure occurred in 17 out of 19 (89.5%) and 9 out of 20 (45%) patients with AUC/MIC <440 and \geq 440, respectively. Finally, it was concluded that AUC/MIC \geq 398 with source specific goals was associated with treatment success (16).

In a retrospective study by Jung et al, MIC values of vancomycin were determined with both BMD and E-test methods in 76 patients with *S. aureus* bacteremia. Most MIC values were in the range of 1-1.49 mg/L. The purpose of this study was to determine the relationship between vancomycin AUC/MIC and treatment failure. Treatment failure with vancomycin was defined as persistent bacteremia (positive blood culture 7 days after initiation of treatment), 30 days all-cause mortality, or recurrence of the bacteremia within 60 days after the completion of therapy. In this study, 20 (26%) patients experienced treatment failure. In the CART analysis, AUC/MIC <430 with E-test method and AUC/MIC <398.5 with BMD method were along with more treatment failures compared to the excess of these breakpoints (50% versus 25% in the E-test method and 45% versus 23.2% in the BMD method, respectively). Achieving AUC/MIC >430 was associated with better clinical outcome (17).

In a retrospective study in 2011, clinical data of 320 patients with *S. aureus* bacteremia were assessed. In this study, 152 (47.5%) patients showed successful outcome and 168 (52.5%) patients experienced treatment failure. The vancomycin MIC values for *S. aureus* isolates were measured using both BMD and E-test methods. Although

the values were between 0.5 mg/L and 2 mg/L, the MIC values obtained from the E-test method were higher than those obtained from the BMD method. The breakpoint of vancomycin AUC/MIC was defined as 421. In patients with AUC/MIC <421, treatment failure was more than that in those with AUC/MIC \geq 421 (61.2% versus 48.6%, respectively). The initial site of MRSA infection was also associated with treatment failure. The highest and the lowest rates of treatment failure were recorded for patients with endocarditis and soft tissue infections, respectively (18).

In another retrospective study by Gawronski et al, 59 patients with MRSA bacteremia and concomitant osteomyelitis were included. This study evaluated the relationship between vancomycin AUC/MIC and time of microbial eradication. Microbial eradication was defined as more than two consecutive negative cultures after the initiation of vancomycin administration. Vancomycin MIC values against these isolates were measured using the E-test method or Microscan. Most of the MIC value measurements were made by the E-test method (85%). Vancomycin MIC values in more than half of the patients were >1 mg/L. In the CART analysis, breakpoint for vancomycin AUC/MIC was determined as 293. Thirty-six (61%) patients had AUC/MIC \leq 293 and 23 (39%) patients had AUC/MIC >293. In univariate analysis, the mean time to microbial clearance was 2 days shorter in patients with AUC/MIC >293 compared to those with AUC/MIC \leq 293. Recurrent bacteremia occurred in 39% of patients with vancomycin AUC/MIC \leq 293 compared to 17% of those with AUC/MIC >293. In this study, only 9% of patients with vancomycin MIC >1 mg/L achieved AUC/MIC >293. In patients with concomitant bacteremia and osteomyelitis who did not reach AUC/MIC >293, time to microbial eradication was 2.5 times longer. Duration of hospitalization in these patients also increased 5 days (19).

Fukumori et al defined area under trough level (AUTL) as a new PK index for the TDM of vancomycin. For calculating this index, the serum trough level of vancomycin was multiplied by 24-hour. In the logistic regression analysis, AUTL had stronger association with vancomycin efficacy compared to AUC_{0-24h}. Optimum breakpoint for AUTL was defined as 331 mg.h/L (20).

Lodise et al examined the association factors of treatment failure in patients with bloodstream infections due to MRSA. Out of 123 patients, 40 (32.5%) had treatment failure. Vancomycin MIC values for MRSA isolates were estimated using the BMD and E-test methods. The MIC values ranged from 0.38 mg/L to 3 mg/L, but the MIC mean value in the E-test method was higher than that in the BMD method. In patients whose MIC values were measured using the BMD method, vancomycin AUC/MIC breakpoint in the first 24 hours of treatment was 521. In this group, 67 patients achieved the target breakpoint, of which 16 (24%) experienced treatment

failure. Among patients who did not reach the breakpoint value, 24 out of 56 (43%) experienced treatment failure. In the second 24 hours of treatment, the vancomycin AUC/MIC ≥ 650 was considered as a breakpoint. Fifteen out of 65 (23%) patients who achieved this target, had treatment failure. However, 25 out of 65 (38.5%) who did not attain this target, experienced treatment failure. In the group whose MIC values were measured by the E-test method, vancomycin AUC/MIC breakpoints in the first and second 24 hours of treatment course were 303 and 320, respectively. Among patients who achieved the first and second target breakpoints, 17 out of 73 (23%) and 21 out of 85 (25%) had treatment failures, respectively. For patients who did not reach these targets, 23 out of 50 (46%) and 19 out of 38 (50%) experienced treatment failure, respectively. Based on the bivariate analysis, risk of treatment failure in patients who achieved the target AUC/MIC breakpoints was 50% less than that in those who did not achieve these goals (21).

In a retrospective study, association between another vancomycin PK/PD index, AUC_{24h}/MBC, and mortality due to *Staphylococcus* bacteremia was investigated. In this study, 53 patients with MRSA bacteremia were evaluated. Vancomycin MIC values against the isolates were measured using both E-test and BMD methods. Moreover, minimum bactericidal concentration (MBC) of vancomycin was measured according to the BMD. The MIC values were between 0.5 and 2 mg/L and the MBC values were within 0.5 to 64 mg/L. MBC/MIC ≥ 32 was defined as vancomycin tolerance. According to the CART analysis, breakpoints of vancomycin AUC_{24h}/MBC and AUC_{24h}/MIC_{BMD} were defined as 176 and 334, respectively. Mortality rate in patients with AUC_{24h}/MIC_{BMD} ≥ 334 was less than that in those who had AUC_{24h}/MIC_{BMD} < 334 (7.7% versus 33.3%, respectively). Additionally, patients with AUC_{24h}/MBC ≥ 176 experienced less mortality rate than those with AUC_{24h}/MBC < 176 (9.4% versus 38.1%, respectively). In the multivariate analysis, only vancomycin AUC_{24h}/MBC ≥ 176 improved survival. Hence, vancomycin AUC_{24h}/MBC might have been a more accurate index for predicting mortality compared to AUC_{24h}/MIC_{BMD} (22).

In one part of the study of Ampe et al, correlations between vancomycin PK/PD parameters and clinical outcomes in patients with different infections were evaluated. The vancomycin AUC/MIC values for microorganisms with MIC > 1 mg/L were defined as 667 and 451 for total and free serum levels of vancomycin, respectively. In patients with AUC_{24h}/MIC < 667 , 3 out of 7 (43%) had treatment failure. However, if AUC_{24h}/MIC > 667 , 2 out of 13 (15%) had treatment failure. Out of 6 patients with AUC_{24h}/MIC < 451 , 3 (50%) patients experienced treatment failure. On the other hand, out of 14 patients with AUC_{24h}/MIC > 451 , only 2 (14%) patients had treatment failure. Vancomycin MIC values

were measured by both BMD and E-test methods. The measured MIC values were in the range of 0.25-2 mg/L (23).

Furthermore, the association between target vancomycin AUC/MIC and mortality was evaluated in patients with MRSA-induced septic shock. In this study, vancomycin MIC value was estimated to be 1 mg/L based on the previous information. According to the data analysis and modelling, 2 vancomycin thresholds viz AUC_{24h}/MIC ≥ 451 and AUC_{24h}/MIC ≥ 578 were defined. Out of the 18 dead patients, only 2 (11%) had AUC/MIC ≥ 578 , and out of the 17 cases that survived, 9 (53%) had AUC/MIC ≥ 578 . The authors concluded that in patients with septic shock, the threshold of 578 for AUC/MIC had a greater clinical benefit than the usual threshold of 400 (24).

In a retrospective study by Martirosov et al, data of 71 patients with MRSA bloodstream infections were included and correlation between vancomycin exposure and treatment failure was evaluated. The vancomycin breakpoints for AUC_{24-48h} and AUC_{24-48h}/MIC were defined as 550 and 336, respectively. In this study, 42 (59%) patients had AUC < 550 mg.h/L and 29 (41%) patients had AUC ≥ 550 mg.h/L. The overall treatment failure was detected in 19 (45%) and 6 (20%) patients with AUC < 550 mg.h/L and AUC ≥ 550 mg.h/L, respectively. The 30-day mortality rates were also 23.80% and 17.24%, respectively. The rates of microbiological failure were 21.42% in patients with AUC < 550 mg.h/L and 10.34% in patients with AUC ≥ 550 mg.h/L. In addition, the recurrence of infection was only observed in 5 (12%) patients with AUC < 550 mg.h/L. MIC values in this study were measured by both the E-test and BMD methods. Sixty-eight (95%) patients had MICE-test = 1.5 mg/L. Two (3%) patients had MICE-test = 2 mg/L and one (1%) patient had MICE-test = 3 mg/L. Both mean MIC₅₀ and MIC₉₀ values were 1 mg/L according to the BMD method. In the Poisson regression analysis, risk of treatment failure in patients with AUC_{24-48h} ≥ 550 mg.h/L was 50% lower than that in those with AUC_{24-48h} < 550 mg.h/L (25).

In the retrospective analysis of data of 139 patients with infective endocarditis (IE) due to MRSA, correlation between vancomycin exposure in day 1 of therapy and treatment failure was evaluated. Treatment failure was defined as bacteremia ≥ 7 days or 30 days infection-related mortality. MIC values were measured by both E-test and BMD methods. In the BMD method, MIC range was 0.5-4 mg/L and in the E-test method, the MIC range was 0.38-4 mg/L. Eighty-five out of 139 patients (61.1%) had MICE-test > 1 mg/L, while 20 out of 139 patients (14.4%) had MIC_{BMD} > 1 mg/L. These values were comparable between with and without treatment failure groups. The vancomycin breakpoints were 600 and 290 for AUC_{0-24h}/MIC_{BMD} and AUC_{0-24h}/MICE-test, respectively. Treatment failure was not significantly different between patients with AUC_{0-24h}/MICE-test ≤ 290 and > 290 .

The median vancomycin C_{min} was 8.4 mg/L in patients with AUC/MIC \leq 600 and 15.2 mg/L in patients with AUC/MIC $>$ 600. Moreover, the median vancomycin C_{min} values were 10.8 and 10.4 mg/L in patients with and without treatment failure, respectively. In this study, 86 (61.8%) patients had AUC/MICBMD \leq 600 and 53 (38.1%) patients had AUC/MICBMD $>$ 600. The overall treatment failure was detected in 89 (64%) patients. Eighty-one out of 139 patients (58.3%) had persistent bacteremia \geq 7 days, and 26 out of 139 patients (18.7%) had 30 days infection-related mortality. The treatment failure was detected in 69.8% and 54.7% of patients with AUC_{0-24h}/MICBMD \leq 600 and $>$ 600, respectively. In the logistic regression analysis, AUC_{0-24h}/MICBMD was an independent risk factor for treatment failure (26).

Studies That Evaluated Correlation Between Vancomycin AUC/MIC and Safety

Frinch et al conducted a retrospective study to compare the consequence of TDM based on AUC and serum trough level in the detection of VIN. Throughout the treatment course, 546 (42.5%) and 734 (57.5%) patients were monitored using the vancomycin serum trough level and AUC, respectively. Based on the bivariate analysis, there was no significant difference in the detection of incidence of VIN between the groups. However based on the multivariate regression analysis, after considering severity of the baseline diseases, concurrent comorbidities and nephrotoxic drugs, vancomycin dosing according to AUC was associated with lower nephrotoxicity. It was found that the median AUC in the AUC-guided group was 471.5 mg.h/L. In addition, vancomycin dosing based on AUC was associated with a 50% reduction in the incidence of VIN (27).

In a retrospective study by Lodise et al on 166 patients, association between vancomycin AUC and its nephrotoxicity was evaluated. During the treatment course, VIN occurred in 21 (12.5%) patients. The mean AUC values were 1318 and 898.5 mg.h/L in patients with and without VIN, respectively. Patients with AUC values \geq 1300 had more episodes of VIN compared to patients with AUC values $<$ 1300 mg.h/L (25.9% versus 10.1%, respectively). Furthermore, in the bivariate analysis, both serum trough concentration and AUC value of vancomycin were predictors of VIN, but in the multivariate analysis, only vancomycin serum trough concentration remained as a predictor (28).

In a multicenter retrospective cohort study, data of 323 patients who received vancomycin were assessed. Indications of vancomycin administration were bacteremia (57%) and pneumonia (43%). The primary outcome was detecting the incidence of VIN in this study. Therefore, most of the patients received at least one other nephrotoxicity with vancomycin. TDM of vancomycin was done in about half (52.3%) of the patients. It was observed that 20 (6%)

patients experienced VIN. The mean vancomycin AUC_{0-48h} values were 1162 and 1413 mg.h/L in patients with and without VIN. The vancomycin AUC_{0-24h} values were also 569 and 700 mg.h/L, respectively. These values for vancomycin AUC_{24-48h} were 577 and 719 mg.h/L. Based on the CART analysis, breakpoints of AUC_{0-48h}, AUC_{24-48h}, and AUC_{0-24h} were 1218, 683, and 677 mg.h/L, respectively. Moreover, AUC_{0-48h} \geq 1218, AUC_{0-24h} \geq 677, and AUC_{24-48h} \geq 683 mg.h/L increased the risk of VIN approximately 4, 4, and 3 folds, respectively. In conclusion, during the first 48 hours of the treatment course, daily vancomycin AUC between 600-800 mg.h/L was associated with nephrotoxicity (29).

In a cohort retrospective study by Chavada et al, association between the incidence of VIN and AUC_{24h} was evaluated in 127 patients. In this study, 20 (15.7%) patients experienced VIN during 2 weeks of treatment course. Based on the CART analysis, vancomycin AUC_{24h} breakpoint was determined as 563 mg.h/L. AUC_{24h} \geq 563 mg.h/L was observed in 20 patients, out of which 8 (40%) were in VIN group and 12 (60%) were in non-VIN group. In this study, AUC_{24h} \geq 563 mg.h/L was an independent predictor of VIN (30).

Studies That Evaluated Correlation Between Vancomycin AUC/MIC and Both Efficacy and Safety

In one study by Suzuki et al, different PK surrogate markers of vancomycin were compared in 31 patients (28 males and 3 females) with pneumonia due to MRSA. Serum trough level, AUC/MIC, and serum peak concentration were considered as monitoring parameters for vancomycin. The primary outcomes of this study were the evaluation of efficacy and safety of vancomycin. Bacterial eradication and VIN were defined as efficacy and safety, respectively. The MIC values obtained by BMD method were in the range of 0.5-1 mg/L. The mean \pm SD of calculated AUC/MIC was also 629.1 \pm 272.8 mg/L. Moreover, the mean \pm SD values of C_{max} and C_{min} were 42.5 \pm 9.9 and 16.3 \pm 6.8 mg/L, respectively. Vancomycin was effective in most patients (74.2%). VIN was defined as an increase in serum creatinine level to more than 0.5 mg/dL or 50% of the baseline value within a few days after the initiation of vancomycin. VIN was detected in 7 out of 31 (22.6%) patients. The analysis showed that AUC_{0-24h} /MIC and AUC_{0-24h} were good predictors of efficacy and safety of vancomycin, respectively. Both AUC_{0-24h} and C_{min} but not C_{max} were equally the predicting indexes of VIN. In all patients, MIC values measured by BMD method were \leq 1 mg/L. Authors concluded that both vancomycin serum trough level and AUC/MIC predicted the efficacy and safety of vancomycin in the same ways (31).

Correlation between vancomycin PK/PD index and efficacy in elderly population (94 patients) with MRSA-induced hospital-acquired pneumonia was evaluated by Mizokami et al in a retrospective study. Vancomycin

MIC values for MRSA isolates were measured using the BMD method. The MIC values were between 0.5 and 2 mg/L and majority of the samples had MIC=1 mg/L. The recommended AUC range for the treatment of hospital-acquired pneumonia caused by MRSA was 250-450 mg.h/L. Thirty-two (34%) patients died. Moreover, 9 (28%) and 3 (5%) patients in survived and non-survived patient groups experienced VIN, respectively. Serum trough concentration of vancomycin was 9.2 mg/L in the survived group and 10 mg/L in the non-survived group. The mean AUC in the survived group was 344 mg.h/L and in the non-survived group was 394.7 mg.h/L. The mortality rate was higher in patients with AUC<250 and AUC>450 mg.h/L compared to patients with AUC values in the range of 250-450 mg.h/L. On the other hand, incidence of VIN in the non-survived group was higher than that in the survived group. In this study, the non-optimal AUC even more than the severity of infection was associated with mortality. A significant difference was also detected in the incidence of VIN between non-survivors (28%) and survivors (4.8%) (32).

Association between serum trough concentration of vancomycin and achievement of AUC/MIC ≥ 400 was investigated in 100 patients with MRSA bacteremia in a retrospective study. In this study, MIC was determined by VITEK-2. Most of the samples had MIC values equal to 1 mg/L (94%) and only one patient had a MIC value of 2 mg/L. In summary, 42 out of 100 (42%) patients achieved AUC/MIC ≥ 400 , and only one (1%) patient who had a MIC value equal to 2 mg/L did not reach the AUC/MIC ≥ 400 (AUC/MIC=162.5). Reaching the serum trough level of 15-20 mg/L compared to 10-14.9 mg/L did not increase the likelihood of reaching the target AUC/MIC. In this study, 22 out of 42 (52%) patients with AUC/MIC ≥ 400 had vancomycin serum trough level less than 15 mg/L. Reaching to AUC/MIC ≥ 400 was not correlated with serum vancomycin trough level and only patients with higher serum vancomycin trough levels experienced VIN. VIN was detected in 9.3% of patients. Mean serum trough concentration of vancomycin was significantly higher in patients with VIN compared to those without VIN (19.5 + 3.6 versus 14.5 + 4.2 mg/L, respectively) (33).

Discussion

Considering global resistance rates among common bugs and restricted treatment options, the optimized use of available antibiotics with regard to PK/PD data is recommended (34). Vancomycin is the commonly-used antibiotic for the treatment of MRSA-related infections. Several PK and PD indexes including serum trough and peak concentrations, AUC, AUTL, MIC, MBC, AUC/MIC, and AUC/MBC have been used for the TDM of vancomycin (10,20,22). The primary goals of TDM are optimizing drug efficacy and increasing patient's safety (35). Despite the introduction of newer antibiotics,

vancomycin is still the preferred medication for MRSA-related infections (3-7). Following a consensus statement in 2009, serum trough concentration has been used for TDM of vancomycin. The recommended target serum trough concentrations were between 15-20 mg/L and 10-15 mg/L for severe and mild to moderate infections, respectively. Achieving the serum trough concentration of 15-20 mg/L was most likely to reach the AUC / MIC ≥ 400 (10).

Association between the serum trough concentration of vancomycin and its efficacy and safety has not been well defined (36). Moreover, in this PK index, susceptibility of microorganism is not considered. Evidence shows that tolerance to vancomycin is increasing (37-39). Accounting the role that susceptibility of microorganisms plays in predicting vancomycin efficacy, a PK/PD parameter (AUC/MIC) may be more accurate TDM indicator than the serum trough concentration (40). On the other hand, recently it has been shown that even with a trough concentration less than 15 mg/L, the target AUC/MIC can be achieved without the increasing risk of VIN. While, serum trough concentration above 15 mg/L was associated with the increased risk of VIN (33).

Few studies have described the correlation between AUC/MIC and its efficacy and safety (14-19,21,26-33). Furthermore, there is no consensus on the target AUC/MIC. Calculation of vancomycin AUC needs multiple blood samplings (41). Although the simplified methods have been adopted on only 2 blood samples, reliability and validity of these methods should be confirmed in different populations (41-42). Most studies have used these simplified methods.

Another issue is the time-point of AUC evaluation. Time to the target concentration of vancomycin was associated with its efficacy. Therefore in most studies, AUC₀₋₂₄ was considered (26,41). However, AUC value during the first 72 hours of treatment course was also correlated with vancomycin effectiveness (24,42).

The commonly used methods for the measurement of MIC of an antibiotic are BMD and E-test (43). As shown in previous studies, the results were different. Although the BMD method is a time consuming process and involves many laboratory staffs, it is a standard method for MIC assessment (44-46).

In predicting clinical outcomes, MIC values obtained by these two methods were not compared in well-designed studies. Only in one study, it was shown that MIC measured by the E-test method was more relevant to the clinical outcome (24). Hence, more studies are required in this regard and data are still scarce.

In the cases with increased MIC, achieving the target AUC/MIC needed further doses of vancomycin and was associated with increased risk of VIN (21).

As vancomycin is commonly used for the treatment of life-threatening infections, exerting its bactericidal activity is

essential. Vancomycin AUC/MBC may be more accurate than AUC/MIC for the prediction of mortality especially when MIC value is significantly different from MBC value (22).

Different cut-off values in the range of 211-650 were defined for vancomycin AUC/MIC (14-19,21,23-26). As AUC/MIC result is dependent on MIC value, each study has defined a specific ratio according to the detected MIC values. Although data in most studies were along with AUC/MIC ≥ 400 , cut-off points less than 400 also showed clinical effectiveness (14,16,19,25).

Concomitant with vancomycin exposure index, severity and source of infection also affect the success of the treatment (16,17). Therefore, greater AUC/MIC values were recommended for patients at higher risk of bacteremia (16), infective endocarditis (26), or septic shock (24).

Limited studies have shown the correlation between vancomycin AUC and incidence of VIN (27-30).

Most of the articles included in this review were retrospective studies. Only 2 out of 20 (10%) studies were prospective. Moreover, different breakpoints for AUC/MIC were defined. In most studies, MIC values were measured using both BMD and E-test methods. As these values were different, the results were not conclusive.

In this respect, further studies are needed to define vancomycin AUC/MIC breakpoint to predict its efficacy and safety.

In most available studies, correlation between vancomycin AUC/MIC and its efficacy and safety were evaluated in the life-threatening infections including bacteremia, endocarditis, and pneumonia. Data regarding less severe infections were rare.

Acute kidney injury and decreased renal function is common in severe infections due to hemodynamic instability and body fluid disturbances (47,48). In most studies in which importance of vancomycin AUC/MIC was evaluated, patients with renal failure were excluded. Hence it seems defining vancomycin AUC/MIC breakpoints in special population including paediatrics, geriatrics, and patients with renal failure should be considered in future studies.

As a new PK surrogate marker, AUTC showed a stronger association with vancomycin efficacy than AUC_{24h} (20). Calculation of this index is easy, and depends on serum trough concentration of vancomycin, and does not require multiple samplings. However, it is a new concept and should be examined in future studies.

Conclusions

Vancomycin has been a known option for the treatment of MRSA-related infections. However, increasing tolerance to vancomycin is a serious concern. The optimized use of vancomycin with regard to its PK and PD properties, therefore, can improve its efficacy and defer the occurrence of tolerance.

Association between the vancomycin PK parameters and its efficacy and safety has not been well defined. Considering the role that microorganism's susceptibility plays in predicting vancomycin efficacy, a PK/PD parameter (AUC/MIC) may be a more accurate indicator than only PK indexes. However, correlation between AUC/MIC and its efficacy and safety have been evaluated in a limited number of studies. Different AUC/MIC values were also targeted.

Future Perspectives

In most available studies, correlation between vancomycin AUC/MIC and its efficacy and safety were evaluated in the life-threatening infections including bacteremia, endocarditis, and pneumonia. However, data regarding less severe infections are rare.

Different AUC/MIC breakpoints were used in previous studies. Therefore, further studies are needed to define vancomycin AUC/MIC breakpoints and in turn to predict its efficacy and safety.

However, data regarding correlation between different PK indexes and VIN are scarce. In this regard, indexes that consider the extent of vancomycin exposure (AUC) might help to predict VIN.

In most studies that evaluated importance of vancomycin AUC/MIC, patients with renal failure were excluded. Therefore, defining vancomycin AUC/MIC breakpoints in special population including paediatrics, geriatrics, and patients with renal failure should be considered in future studies.

Ethical Approval

Not applicable.

Conflict of Interest Disclosures

None.

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