Vancomycin minimum inhibitory concentration, host comorbidities and mortality in *Staphylococcus aureus* bacteraemia

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Abstract

We reported an association between elevated vancomycin MIC and 30-day mortality in patients with *Staphylococcus aureus* bacteraemia (SAB), including patients with methicillin-susceptible *S. aureus* (MSSA) treated with flucloxacillin. A detailed analysis of comorbidities and disease severity scores in the same cohort of patients was performed to ascertain if unknown clinical parameters may have influenced these results. The association between elevated vancomycin MIC and 30-day mortality in SAB remained significant (p 0.001) on multivariable logistic regression analysis even when accounting for clinical factors. In addition, the association persisted when restricting analysis to patients with MSSA bacteraemia treated with flucloxacillin. This suggests that elevated vancomycin MIC is associated with but not causally linked to an organism factor that is responsible for increased mortality.

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Background

In a previous study we demonstrated an association between elevated vancomycin MIC and 30-day all-cause mortality in a large cohort of patients with *Staphylococcus aureus* bacteraemia (SAB) in Australia and New Zealand that was independent of the methicillin susceptibility of the blood culture isolate or antibiotic treatment received [1]. However, it is uncertain whether this association was confounded by clinical parameters not available at the time of our initial publication. Elevated vancomycin MIC within the susceptible range has not been uniformly associated with poor outcome [2], and differing comorbidities may potentially explain this observation. Therefore we chose to search for potential hidden clinical confounders in our cohort of patients to determine whether we could explain differences that we had previously observed in 30-day survival.

Materials and Methods

Study population

The study population was derived from our previously described cohort of adult and paediatric patients hospitalized

with SAB in Australia and New Zealand at eight sites [1]. Patients were divided into two groups according to whether their initial *S. aureus* blood culture isolate had a low or elevated vancomycin MIC within the susceptible range, defined as Etest® ≤1.5 mg/L or >1.5 mg/L, respectively. The main outcome measure was 30-day all-cause mortality from the date of the first positive (index) blood culture. We also analysed 30-day attributable mortality as defined by Lodise *et al.* [3].

Data collection

Extensive clinical data were collected retrospectively using chart review: heart disease (including ischaemic heart disease, cardiac failure, arrhythmia requiring insertion of permanent pacemaker or implantable cardioverter-defibrillator), end-stage kidney disease, receipt of haemodialysis, diabetes mellitus, dementia, chronic liver disease, malignancy (haematological or solid organ), transplantation (haematological or solid organ), receipt of chemotherapy, immunosuppression or corticosteroids (with an equivalent daily dose of ≥20 mg prednisone), human immunodeficiency virus infection and active injecting drug use were assessed as individual comorbidities. We assessed comorbidity burden using the Charlson Comorbidity Index (CCI) [4] and presence of 'Do Not Resuscitate' (DNR) orders. Disease severity at onset of SAB was measured using intensive care unit (ICU) -validated scores: Acute Physiology And Chronic Health Evaluation (APACHE) II, Simplified Acute Physiology Score (SAPS) II and the Pitt bacteraemia score [5], a bacteraemia-validated method. Other data obtained included ICU admission and renal function at SAB onset. For data analysis, dichotomous variables for CCI and disease severity scores were also created using values associated with inferior outcomes in the published literature (APACHE II ≥18 [6], SAPS II >45 [7], CCI ≥3 [4], Pitt bacteraemia score ≥4 [8]).

Microbiological data

The index blood culture isolate from each patient was stored at −80°C and underwent detailed microbiological testing as previously described [1]. Briefly, this included vancomycin MIC using broth microdilution [9] and Etest® (bioMérieux, Marcy l'Etoile, France) methodologies, and screening for vancomycin heteroresistance was performed using the Glycopeptide Resistance Detection Etest® (bioMérieux, Marcy l'Etoile, France).

Statistical analysis

The chi-square test or Fisher exact test was used to compare categorical variables, and the Student's *t*-test or Mann–Whitney *U* test was used for continuous variables. Potentially significant variables on univariable analysis ($p < 0.2$) were considered *a priori* for inclusion in a multivariable logistic regression model. Pairwise correlation coefficients were examined between variables that were potentially related before inclusion in our multivariable model to avoid collinearity. Stepwise backward elimination was performed and variables with $p < 0.05$ were retained in the final multivariable model. The Hosmer–Lemeshow statistic was performed to test the goodness of fit of the final model. A p-value of <0.05 was considered statistically significant, and analysis was performed using STATA v11.1 (StataCorp, College Station, TX, USA).

Ethics

Human ethics committee approval was obtained at each of the participating sites.

Results

Demographics

Expanded clinical data were available for 418 patients from our original cohort (78.6%), with 30-day mortality data available in 410 patients. Demographics, comorbidities and disease severity scores are summarized in Table 1 according to vancomycin MIC group (low versus elevated but within the susceptible range) and 30-day mortality. Overall the mean age (± SD) of our patients was 57.8 ± 21.4 years. The median duration of bacteraemia was 1 day (interquartile range 1–2 days). DNR orders were documented in 101/373 (27.1%) patients, more than a third of which were recorded before a diagnosis of SAB (38/101, 37.6%). Attributable 30-day mortality was 10.7% (44/410) compared with all-cause mortality (18.0%, 74/410), and elevated vancomycin MIC was statistically associated with both attributable and all-cause mortality ($p < 0.001$ and p 0.002, respectively).

Patients with elevated vancomycin MIC were more likely to have hospital onset bacteraemia, to have infection with methicillin-resistant *S. aureus* (MRSA), to receive treatment with vancomycin and to have higher mortality. At 30 days, non-survivors were older and more likely to experience hospital-onset bacteraemia, ICU admission, sepsis syndrome and have an isolate with an elevated vancomycin MIC.

Effect of individual comorbidities

The presence of heart disease (as defined above), diabetes mellitus, end-stage kidney disease and malignancy was common in our cohort (34.2%, 26.3%, 16.0%, 20.1%, respectively; Table 1). Malignancy was associated with both elevated vancomycin MIC (p 0.009) and 30-day mortality (p 0.037) but not 30-day attributable mortality (p 0.428). Heart disease was associated with mortality (p 0.001) but not elevated vancomycin MIC.

TABLE 1. Demographics, comorbidities and disease severity scores for 418 patients with *Staphylococcus aureus* bacteraemia

	Vancomycin MIC group (*n* = 418)			30-day outcome (*n* = 410)		
Variable	**Low[a] (*n* = 280)**	**Elevated[a] (*n* = 138)**	**p value**	**Alive (*n* = 336)**	**Dead (*n* = 74)**	**p value**
Demographics						
Age ≥70 years	94 (33.6)	54 (39.1)	0.278	101 (30.1)	45 (60.8)	<0.001
Age <18 years	11 (3.9)	6 (4.4)	0.798	15 (4.5)	1 (1.4)	0.324
Male sex	198 (70.7)	93 (67.4)	0.499	233 (69.4)	52 (70.3)	1.000
Hospital onset	105 (37.5)	75 (54.4)	0.001	136 (40.5)	41 (55.4)	0.020
Methicillin-resistant *S. aureus*	77 (27.5)	70 (50.7)	<0.001	112 (33.3)	33 (44.6)	0.081
Device-associated	114/262 (43.5)	67/133 (50.4)	0.202	149/319 (46.7)	29/69 (42.0)	0.508
Intensive care unit admission	79/278 (28.4)	41/136 (30.2)	0.730	87/332 (26.2)	31/74 (41.9)	0.010
Acute renal failure	60/276 (21.7)	37/137 (26.3)	0.323	72/331 (21.8)	24/74 (32.4)	0.069
Principal clinical manifestation						
Infective endocarditis	29 (10.4)	8 (5.8)	0.145	32 (9.5)	4 (5.4)	0.364
Osteoarticular	29 (10.4)	11 (8.0)	0.484	33 (9.8)	6 (8.1)	0.827
Skin and skin structure	37 (13.2)	24 (17.4)	0.302	49 (14.6)	9 (12.2)	0.713
Sepsis syndrome	23 (8.2)	18 (13.0)	0.161	24 (7.1)	17 (23.0)	<0.001
Pneumonia	15 (5.4)	8 (5.8)	0.823	17 (5.1)	6 (8.1)	0.276
Vancomycin treatment	108 (38.6)	79 (57.3)	<0.001	148 (44.1)	38 (51.4)	0.302
Outcomes						
Elevated vancomycin MIC[a]	NA	NA	NA	96 (28.6)	39 (52.7)	<0.001
30-day all-cause mortality	35/275 (12.7)	39/135 (28.9)	<0.001	NA	NA	NA
30-day attributable mortality	20/275 (7.8)	24/135 (17.8)	0.002	NA	NA	NA
Persistent bacteraemia[b]	17/216 (7.9)	8/115 (7.0)	0.831	18/269 (7.0)	7/56 (12.5)	0.165
Recurrent bacteraemia[c]	20/269 (7.4)	9/133 (6.8)	1.000	25/328 (7.6)	4/71 (5.6)	0.801
Comorbidities						
Heart disease	95 (33.9)	48 (34.8)	0.913	102 (30.4)	38 (51.4)	0.001
Diabetes mellitus	76 (27.1)	34 (24.6)	0.637	90 (26.8)	20 (27.0)	1.000
End-stage kidney disease	45 (16.1)	22 (15.9)	1.000	59 (17.6)	8 (10.8)	0.169
Haemodialysis	39/279 (14.0)	21/136 (15.4)	0.766	53 (15.8)	7 (9.5)	0.204
Dementia	13 (4.6)	4 (2.9)	0.599	13 (3.9)	4 (5.4)	0.523
Chronic liver disease	34 (12.1)	13 (9.4)	0.511	33 (9.8)	11 (14.9)	0.215
Malignancy	46 (16.4)	38 (27.5)	0.009	61 (18.2)	22 (29.7)	0.037
Transplantation	11 (3.9)	6 (4.3)	0.798	17 (5.1)	0 (0.0)	0.051
Immunosuppression	35 (12.5)	21 (15.2)	0.448	50 (14.9)	6 (8.1)	0.138
HIV infection	3 (1.1)	1 (0.7)	1.000	4 (1.2)	0 (0.0)	1.000
Active injecting drug use	21 (7.5)	5 (3.6)	0.137	25 (7.4)	0 (0.0)	0.012
Comorbidity burden						
CCI						
Mean ± SD	1.6 ± 1.5	2.0 ± 1.7	0.015	1.6 ± 1.5	2.3 ± 1.7	0.003
Score ≥3 [4]	72 (25.7)	51 (37.0)	0.022	93 (27.7)	29 (39.2)	0.067
DNR order	50/248 (20.2)	51/125 (40.8)	<0.001	41/291 (14.1)	60/74 (81.1)	<0.001
Disease severity scores						
APACHE II						
Mean ± SD	14.2 ± 6.6	15.4 ± 6.8	0.084	13.6 ± 6.4	19.3 ± 6.2	<0.001
Score ≥18 [6]	79 (28.2)	50 (36.2)	0.115	90 (26.8)	39 (52.7)	<0.001
SAPS II						
Mean ± SD	25.4 ± 10.9	28.0 ± 12.5	0.030	24.4 ± 10.7	35.4 ± 10.8	<0.001
Score >45 [7]	18 (6.4)	12 (7.6)	0.423	20 (6.0)	10 (13.5)	0.044
Pitt bacteraemia score						
Mean ± SD	2.6 ± 1.8	2.8 ± 1.9	0.295	2.5 ± 1.7	3.4 ± 2.3	<0.001
Score ≥4 [8]	56 (20.0)	33 (23.9)	0.375	59 (17.6)	29 (39.2)	<0.001

Data are expressed as number (%) unless otherwise specified.
p value calculated using Fisher's exact test or Student's *t*-test where appropriate.
APACHE, Acute Physiology And Chronic Health Evaluation; CCI, Charlson Comorbidity Index; DNR, Do Not Resuscitate; HIV, human immunodeficiency; virus; NA, not assessed; SAPS, Simplified Acute Physiology Score; SD, standard deviation.
[a]Elevated vancomycin MIC defined as Etest® >1.5 mg/L.
[b]Defined as positive blood culture for SAB 7 days or more after index blood culture.
[c]Defined as new positive SAB within 30 days of index blood culture after documentation of negative blood cultures.

Effect of comorbidity burden

Patients with elevated vancomycin MIC had a higher number of comorbidities (specifically CCI ≥3 and DNR orders, Table 1), suggesting that multiple comorbidity burden may be a potential confounder influencing the observed association between increased vancomycin MIC and mortality. As expected, high comorbidity burden was associated with increased mortality.

Effect of disease severity scores

Disease severity score measures were similar in the low and elevated vancomycin MIC groups using both ICU and bacteraemia scores at onset of SAB, although there was a tendency towards higher APACHE II and SAPS II scores with elevated vancomycin MIC. As expected, all disease severity scores were higher in non-survivors, either using the raw numerical score or the dichotomized category.

Factors associated with 30-day mortality

To determine how these comorbidity variables impacted on the association between elevated vancomycin MIC and mortality, we used a multivariable logistic regression model. We considered including variables with univariate p <0.2 for multivariable analysis; however, we only selected variables with univariate p <0.05 for inclusion into our logistic regression model because of sample size considerations (Table 2). In addition, variables that were correlated were not entered

TABLE 2. Univariable and multivariable logistic regression analysis for associations with 30-day mortality (n = 410)

Variable[a]	Univariable p value	Multivariable OR	95% CI	p value
Age ≥70 years	<0.001	3.73	2.14–6.51	<0.001
Elevated vancomycin MIC[b]	<0.001	2.59	1.49–4.51	0.001
Pitt score ≥4	<0.001	2.79	1.54–5.06	0.001
Sepsis syndrome	<0.001	3.28	1.53–7.03	0.002
CCI	0.003			NS
ICU admission	0.010			NS
Active injecting drug use	0.012			NS
Hospital onset	0.020			NS

CCI, Charlson Comorbidity Index; NS, not significant (p ≥0.05).
[a]As discussed in Results section, variables that were significant on univariable analysis that were not considered for multivariable analysis were presence of a Do not resuscitate order (direct effect on outcome due to treatment modification), APACHE II score ≥18 and SAPS II score (collinearity with age), heart disease and malignancy (collinearity with CCI).
[b]Elevated vancomycin MIC defined as Etest® >1.5 mg/L.

twice in the model. For example, age is a component of the APACHE II and the SAPS II scores and so these variables were not included together. In contrast, age is not required for calculation of the Pitt bacteraemia score so both these variables could be considered. Specific comorbidities such as heart disease and malignancy are components of the CCI. Although DNR orders were strongly associated with mortality, we did not consider this variable for inclusion in our multivariable model because DNR orders result in treatment modification or complete cessation that directly impacts on patient outcome. Using backward stepwise elimination, parameters that were significantly associated with 30-day mortality were age ≥70 years, sepsis syndrome, elevated vancomycin MIC and Pitt bacteraemia score ≥4 (Table 2). That is, even when adjusting for these potential clinical confounders, our original association between elevated vancomycin MIC and mortality in SAB still remained significant. The final logistic regression model appeared robust (Hosmer–Lemeshow statistic, p 0.981). When we substituted age ≥70 years with an acute physiology score (either APACHE II or SAPS II), elevated vancomycin MIC remained significant in the final model (data not shown). When we included DNR orders in our multivariable analysis for 30-day mortality, only sepsis syndrome (p <0.001) and DNR orders (p <0.001) were significant in the final model. DNR orders were more strongly correlated with 30-day mortality (Spearman r = 0.602) than elevated vancomycin MIC (Spearman r = 0.219).

Thirty-day attributable mortality (instead of all-cause mortality) was associated with elevated vancomycin MIC as well as age ≥70 years and sepsis syndrome in a similar multivariable logistic regression model (p 0.007, p 0.005, p 0.034, respectively); a Pitt bacteraemia score ≥4 did not achieve statistical significance (p 0.053). When we restricted the multivariable analysis to the sub-group of patients with methicillin-susceptible *S. aureus* (MSSA) bacteraemia who were treated with flucloxacillin, the association between elevated vancomycin MIC and mortality persisted (p 0.001); age ≥70 years and sepsis syndrome were also significant in the model (p <0.001 and p 0.019 respectively).

Discussion

We have previously reported that in patients with SAB, elevated vancomcyin MIC within the susceptible range is associated with increased 30-day mortality. This finding remained significant even in the subgroup of patients with SAB due to MSSA who received flucloxacillin treatment, suggesting that vancomycin MIC is a marker of host or pathogen determinants rather than being causally associated with poor outcome. Here, we have enriched our cohort by including a range of new clinical data to examine whether host factors may have explained the difference in mortality that we initially observed.

Subtle elevations in the vancomycin MIC within the susceptible range have been increasingly linked to mortality and other inferior outcomes in SAB [2,10]. This finding, however, is not consistent among all publications [11]. Differences in MIC methodology and MIC values [2] associated with these poor outcomes, as well as the potential impact of the timing of isolate testing [12], make clinical interpretation and application difficult. Recent MRSA treatment consensus guidelines suggest that a patient's clinical and microbiological response should guide clinicians about continuing vancomycin treatment, rather than a specific vancomycin MIC result [13]. Vancomycin susceptibility is undoubtedly important in treatment outcome when strains are intermediate or resistant (broth microdilution MIC >2 mg/L), and it is difficult to achieve target pharmacokinetic–pharmacodynamic measures in vancomycin-treated patients using recommended dosing regimens when the vancomycin MIC is ≥2 mg/L [14].

We found that the inclusion of a range of additional comorbid conditions generally had little impact on outcome. Measures of comorbidity burden, such as the CCI, or specific individual comorbidities, such as malignancy, were linked to vancomycin MIC and outcome on univariable analysis but failed to remain significant in the final multivariable model. As expected, disease severity scores were strongly associated with mortality. Yet despite considering these variables, the original relationship we observed between elevated vancomycin MIC and mortality persisted. Moreover, this relationship still existed in patients with MSSA bacteraemia who were treated with flucloxacillin, strengthening our contention that elevated vancomycin MIC is a marker rather than a root cause

of the increased mortality observed in patients with SAB caused by isolates with high-normal vancomycin MIC.

We had excluded DNR orders when analysing possible predictors of 30-day mortality in our multivariable analysis because of the direct impact on mortality from treatment modifications or cessation. When we included DNR orders in an alternative multivariable logistic stepwise regression model, elevated vancomycin MIC was the last variable to be eliminated before the final model was obtained. Although DNR orders and elevated vancomycin MIC were both strongly associated with 30-day mortality on univariable analysis, DNR orders were more strongly correlated compared with elevated vancomycin MIC and may potentially reflect a more complicated group of adverse prognostic markers. Clinical variables that have been previously associated with the use of DNR orders (such as age, malignancy, increased illness severity scores, residence in long-term care facilities [15,16]) are similar nonetheless to those that were associated with elevated vancomycin MIC. As patients with these characteristics are more likely to have frequent healthcare attendances, they may be exposed to *S. aureus* strains or clones adapted to healthcare settings that have higher vancomycin MIC (especially as hospital-onset bacteraemia and MRSA were also associated with elevated vancomycin MIC).

We hypothesize that elevated vancomycin MIC is a marker of an unknown organism factor or host–pathogen interaction that predicts mortality. Aguado *et al.* [17] recently reported a similar finding with higher rates of complicated bacteraemia in patients with MSSA bacteraemia if the isolates had elevated vancomycin MIC. Multiple studies have highlighted an association between bacterial factors such as genotype and other potential virulence determinants and outcome in *S. aureus* infections [18,19]. Bacterial genotype has been associated with elevated vancomycin MIC [20] as well as risk of infective endocarditis in MRSA bacteraemia [21]. Healthcare-adaptation of *S. aureus* strains and successful clones (not merely limited to MRSA) may be an important determinant, especially as there may be cumulative exposure in the older population. We also observed that non-survivors in our cohort had higher rates of sepsis syndrome and disease severity scores at onset of bacteraemia, probably reflecting a host–pathogen interaction involving some of these determinants.

Limitations of this study include the retrospective collection of the new clinical data that we included, and the absence of detailed organism testing to attempt to identify a virulence determinant in the laboratory that could explain the enhanced virulence that we observe clinically. It is possible that our final multivariable model was affected by excluding co-dependent variables; however, performance of *post-hoc* analysis that substituted some of these variables (such as replacing age $\geq$ 70 years with APACHE II score) did not alter the outcome of the final model.

We found that the association between elevated vancomycin MIC and 30-day mortality in patients with SAB persisted after adjustment for possible clinical confounders, including patients who were not treated with vancomycin. We hypothesize that host–organism interactions or exposure to healthcare-adapted *S. aureus* strains may explain this association. Additional studies are required to explore the importance of subtle variations in virulence that appear to be important determinants of mortality from *S. aureus* bacteraemia.

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Conference Presentation

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Transparency Declaration

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