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Early empirical glycopeptide therapy for patients with methicillin-resistant *Staphylococcus aureus* bacteraemia: impact on the outcome

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***Objectives*: To evaluate whether appropriate early empirical glycopeptide therapy improves outcomes of patients with methicillin-resistant *Staphylococcus aureus* (MRSA) bacteraemia.**

***Methods*: We retrospectively collected the data for all adult patients with confirmed MRSA bacteraemia diagnosed and treated at National Taiwan University Hospital during the period 1 April 1997–31 March 2001, and followed their survival up to three years. The main outcome measures were MRSA-related death and all-cause mortality.**

***Results*: There were 77 MRSA-related deaths among 162 patients. There was no statistically significant difference in MRSA-related deaths between patients receiving glycopeptides before or within 48 h after blood culture ($n = 43$) (55%, 18/33, non-septic shock group; 90%, 9/10, septic shock group) or those whose glycopeptide therapy was begun more than 48 h after blood culture ($n = 119$) (37%, 40/107, non-septic shock group; 83%, 10/12, septic shock group) ($P = 0.11$ and 1.00, respectively). The outcome measure of all-cause mortality from 30 days to 3 years yields similar results. Multivariate logistic regression analysis and Cox analysis showed that the length of delay (daily increment) between blood culture sampling and start of glycopeptide therapy did not have a statistically significant impact on MRSA-related death or all-cause 30-day mortality after adjusting for the effect of other variables [adjusted odds ratio 0.99, 95% confidence interval (95% CI) 0.88–1.12; adjusted hazard ratio 0.87, 95% CI 0.74–1.02, respectively).**

***Conclusions*: The hypothesis that earlier empirical use of glycopeptide therapy reduces mortality in patients with hospital-acquired MRSA bacteraemia was not supported.**

Keywords: vancomycin, teicoplanin, nosocomial infections, prognosis

Introduction

The incidence of hospital-acquired methicillin-resistant *Staphylococcus aureus* (MRSA) infection has increased dramatically in many countries,[1–7] with fatality rates for patients who develop bacteraemia as high as 20–50%.[8–11] Clinicians treating patients with hospital-acquired infections face the dilemma of whether to prescribe glycopeptides as part of an initial empirical regimen before culture results become available. Because of the danger of worsening the problem of emerging vancomycin-resistant Gram-positive bacteria,[12,13] an aggressive approach in empirical use of glycopeptides needs to be justified by evidence of its effectiveness.

Surprisingly, it remains unclear whether appropriate early empirical therapy with a glycopeptide actually improves outcomes of patients with hospital-acquired MRSA infection. Three observational studies investigating the role of empirical glycopeptide

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therapy in treatment of MRSA bacteraemia have been published, with contradictory results.[14–16] Although a randomized trial using placebo in a control group is the best way to reach an unbiased conclusion, such trials may not be ethical because empirical glycopeptide therapy is already widely assumed to be life-saving.[17,18]

We hypothesized that use of a careful study design,[19] involving only MRSA patients with control of the sepsis severity and other risk factors for mortality, would allow an observational study to demonstrate the theoretical benefit of earlier glycopeptide therapy after follow-up for 3 years.

Methods

Setting

This study was conducted at National Taiwan University Hospital (Taipei, Taiwan). The hospital is a university-affiliated medical centre with a 2000 bed capacity that provides both primary and tertiary referral care. Vancomycin and teicoplanin, the two glycopeptides available at our institution, were not used for surgical prophylaxis during the study period except for the rare patients who had a history of anaphylaxis to β-lactams. However, there was no restriction on the therapeutic use of glycopeptides.

Study design

We retrospectively collected the data for all adult patients with confirmed MRSA bacteraemia diagnosed and treated from 1 April 1997 to 31 March 2001. During this period, vancomycin and teicoplanin were the only two intravenous agents appropriate for treatment of MRSA bacteraemia; quinupristin/dalfopristin and linezolid were not available at that time. The survival status of patients included in this analysis was followed until 31 March 2004.

Patients were classified into the non-empirical glycopeptide group or the empirical glycopeptide group based on whether glycopeptide therapy was begun more than 48 h after blood culture sampling. MRSA-related deaths, all-cause mortality, and length of hospital stay, from the time of first MRSA-positive blood culture to discharge (or death) were compared between the two groups. We also used time interval as a continuous variable—from the first blood sampling that demonstrated MRSA bacteraemia to the start of glycopeptide therapy—as a potential explanatory variable in multivariate analysis.

Microbiology

Culture, identification, and susceptibility testing of MRSA isolates were performed according to standard microbiological methods.[20,21] BACTEC (Becton Dickinson, Spark, MD, USA) automated bacterial blood culture systems have been used since 1986 at our institution to facilitate rapid identification and reporting. Since January 2000, the clinical microbiology laboratory has routinely screened clinical MRSA isolates using brain–heart infusion agar supplemented with vancomycin 4 mg/L to detect *S. aureus* strains with reduced susceptibility to vancomycin.[22]

Inclusion criteria

The list of all adult patients (age ≥ 16 years) in whom MRSA had been isolated from blood was obtained using the hospital computer database of clinical bacterial isolates. Because inclusion of patients without true MRSA bacteraemia would diminish the measured beneficial effect of empirical glycopeptide therapy, only patients with MRSA isolated from two blood cultures taken from two different peripheral sites were included in the analysis as confirmed MRSA bacteraemia cases. Similarly, patients with concomitant fungaemia or bacteraemia caused by other bacteria were excluded in order to avoid potential bias.

Clinical data

For each included case, demographic and clinical information was obtained from medical records. Survival data after hospital discharge were obtained from medical records in the outpatient department and the official death registration database[23] (Department of Health, Executive Yuan, Taiwan), which recorded the date of death of all Taiwanese citizens.

Severity of bacteraemia

Severity of MRSA bacteraemia on the day of positive blood culture sampling was assessed by severity of sepsis syndrome[24] and APACHE II scores.[25] To enhance applicability of the APACHE II scoring system to the present patient group, a modification allowed zero points to be assigned to the items 'PaO_2' and 'pH' if the attending physicians did not perform arterial blood gas analysis due to absence of cyanosis or respiratory distress.

Severity of underlying diseases

Severity of underlying disease before the onset of hospital-acquired MRSA infection was classified by McCabe–Jackson criteria.[26] Specifically, leukaemia or lymphoma refractory to chemotherapy and advanced-stage cancer that made patients bedridden despite available treatment were all classified as rapidly fatal. Uraemia requiring dialysis, decompensated liver cirrhosis, congestive heart failure, chronic respiratory failure requiring mechanical ventilatory assistance, aplastic anaemia and malignant diseases that cannot be cured but did not match the above-stated criteria for rapidly fatal diseases were classified as ultimately fatal. Other conditions were classified as non-fatal.

MRSA-related mortality

Death was considered to be related to MRSA infection if one or more of the following criteria[15] were present: blood cultures were positive for MRSA at the time of death; death occurred before resolution of signs and symptoms of MRSA infection; death occurred not more than 14 days after onset of MRSA bacteraemia without another explanation for cause of death.

Statistical analysis

The Kaplan–Meier survival curve was used to analyse survival probability after the day of the first blood culture positive for MRSA. Log-rank test, Fisher's exact test and Mann–Whitney test were used to compare survival curves, binary variables and continuous variables, respectively. Multivariate analysis was conducted using either Cox's proportional hazards model, if the proportional assumption was applicable, or logistic regression model. The statistical software used for computation was S-PLUS 2000 for Windows (MathSoft Inc., MA, USA). Two-tailed P values of <0.05 were considered to be statistically significant.

Results

Characteristics of patients

From 1 April 1997 to 31 March 2001, a total of 162 adult patients with confirmed MRSA bacteraemia—but without concomitant fungaemia or bacteraemia caused by other bacteria—were diagnosed and treated. All 162 cases involved hospital-acquired infection (Table 1). The average delay (days) in start of glycopeptide therapy was 0 days (median, range: 0–1 days) in

Table 1. Characteristics of 162 patients with hospital-acquired MRSA bacteraemia

Characteristics	Number (%)		
	Empirical glycopeptide group[a] (n = 43)	Non-empirical glycopeptide group (n = 119)	P value
Delay (days) in start of glycopeptide therapy, median (range)	0 (0–1)	3 (2–29)	<0.01**
Age, years median (range)	70 (35–92)	67 (18–99)	0.34
Age ≥60 years	31 (72)	75 (63)	0.35
Gender, male	30 (70)	71 (60)	0.27
HIV seropositive	0 (0)	2 (2)	1.00
Neutropenia (<500/mm^3)	4 (9)	9 (8)	0.75
Immunosuppressive therapy[b]	10 (23)	31 (26)	0.84
Alcoholism	2 (5)	4 (3)	0.66
Diabetes mellitus	10 (23)	35 (29)	0.55
Chronic heart disease[c]	10 (23)	32 (27)	0.69
Chronic lung disease[d]	6 (14)	14 (12)	0.79
Uraemia requiring dialysis	11 (26)	34 (29)	0.84
Decompensated liver cirrhosis[e]	9 (21)	11 (9)	0.06
Malignancies	13 (30)	33 (28)	0.84
McCabe classification			
Rapidly fatal	7 (16)	14 (12)	0.44
Ultimately fatal	22 (51)	67 (56)	0.56
Non-fatal	14 (33)	38 (32)	1.00
APACHE II score[f], median (range)	19 (1–31)	17 (2–37)	0.23
APACHE II score ≥15	31 (72)	80 (67)	0.70
Severity of SIRS[f]			
Septic shock	10 (23)	12 (10)	0.04**
Severe sepsis	3 (7)	9 (8)	1.00
Sepsis	29 (67)	92 (77)	0.22
No sepsis	1 (2)	6 (5)	0.68
Site of MRSA infection[g]			
Endocarditis	2 (5)	5 (4)	1.00
Meningitis	0 (0)	1 (1)	1.00
Pneumonia	8 (19)	20 (17)	0.82
Catheter-related infection	20 (47)	52 (44)	0.86
Urinary tract infection	2 (5)	3 (3)	0.61
Soft tissue infection	13 (30)	23 (19)	0.20
Osteomyelitis	2 (5)	8 (7)	1.00
No obvious source	7 (16)	24 (20)	0.66

MRSA, methicillin-resistant *S. aureus*; HIV, human immunodeficiency virus; SIRS, systemic inflammatory response syndrome.
[a]Empirical glycopeptide group: patients began glycopeptide therapy before or within 48 h after blood culture sampling.
[b]Cytotoxic chemotherapy, corticosteroid or ciclosporin.
[c]Symptomatic coronary artery disease or congestive heart failure.
[d]Chronic obstructive pulmonary disease, bronchiectasis, or pneumoconiosis.
[e]With physical evidence of portal hypertension.
[f]At time of blood culture sampling.
[g]Some patients had more than one infected site.
**Statistically significant ($P < 0.05$).

empirical glycopeptide therapy group (n = 43) versus 3 days (median, range: 2–29 days) in the non-empirical glycopeptide group (n = 119) ($P < 0.01$). Patients in the empirical glycopeptide group were twice as likely to have septic shock at time of blood culture sampling as patients in the non-empirical glycopeptide group (23% versus 10%; P = 0.04). There was no significant difference in age, gender, sites of MRSA infection, and types and severity of underlying diseases between the two groups (Table 1).

Empirical antimicrobial therapy

Of the 162 patients, all but three received empirical antimicrobial therapy after blood culture sampling. The chosen agents, alone or in combination, included various β-lactams and aminoglycosides, vancomycin, teicoplanin, ciprofloxacin, trimethoprim/sulfamethoxazole, clindamycin, metronidazole, and erythromycin. Among the 43 patients in the empirical glycopeptide group, 37 received vancomycin and 6 received teicoplanin in their

empirical regimens. None of the agents used in the empirical regimens of the other 119 patients were active *in vitro* against MRSA.

Definite antimicrobial therapy

By routine susceptibility test, all of the MRSA strains isolated from included patients were susceptible to both vancomycin and teicoplanin (see the Appendix for more details). The interval from blood culture sampling to receipt of results ranged from 2 to 7 days. After reporting of blood culture results, the 43 patients in the empirical glycopeptide group continued to receive their initial vancomycin or teicoplanin therapy, and 107 of the 119 patients in the non-empirical glycopeptide group started to receive vancomycin (104 patients) or teicoplanin (three patients). In the non-empirical glycopeptide group, 12 patients did not receive glycopeptide therapy, and 10 of them died before the blood culture report became available. The remaining two patients did not receive glycopeptide therapy for unspecified reasons.

During the course of treatment, 13 patients (four in the empirical glycopeptide group and nine in the non-empirical glycopeptide group) developed skin rash or leucopenia under vancomycin therapy, necessitating a change to teicoplanin. Among patients who survived for more than 7 days, duration of glycopeptide therapy ranged from 7 days to 6 weeks, depending on clinical response and whether endocarditis or osteomyelitis was present.

Timing and administration of glycopeptide therapy

Glycopeptide therapy was started before blood culture sampling in 11 patients due to fever and isolation of MRSA from non-blood sites such as sputum or wound. The interval between blood culture sampling and first dose of glycopeptide was 0–24 h in 16 patients, 24–48 h in 16 patients, 48–72 h in 35 patients, 72–96 h in 38 patients, 96–120 h in 19 patients, 120–144 h in six patients, 144–168 h in four patients and >168 h in five patients. The routine dosage and administration of vancomycin was either 15 mg/kg every 12 h or 7.5 mg/kg every 6 h, with adjustment for renal function, infused at a rate of 500 mg/h. The routine dosage and administration of teicoplanin was 12 mg/kg loading then 12 mg/kg/day for endocarditis/septic arthritis or 6 mg/kg/day for other infections, with adjustment for renal function, infused over 30 min.

During the study period, 21 patients who did not have septic shock (20 in the non-empirical glycopeptide group and one in the empirical glycopeptide group) were enrolled into a clinical trial and given an initial loading dose of 25 mg/kg vancomycin, infused at a rate of 500 mg/h, followed by the standard regimen. The delay in start of glycopeptide therapy was 3.5 days (median, range: 2–5 days) in these 20 non-empirical-glycopeptide-group patients, and 1 day in the empirical-glycopeptide-group patient, respectively.

Serum vancomycin levels

The median trough vancomycin levels were 10.1 (range: 8.4–45.6) mg/L among empirical glycopeptide therapy group versus 12.5 (range: 4.8–27.6) mg/L among non-empirical glycopeptide therapy group, without significant difference between two groups (P = 0.55). The median peak vancomycin levels were 20.1 (range: 11.1–58.6) mg/L versus 25.7 (range: 12.6–74.0) mg/L, without significant difference either (P = 0.93). After the loading dose, the 21 patients who were given 25 mg/kg vancomycin loading dose had a median 1 h post-loading serum vancomycin level of 26.2 (range: 5.8–51.3) mg/L.

Outcome and prognostic factors

The all-cause mortality rate was 36% (59/162) on day 30, with a gradual increase to 75% (122/162) at the end of the 3 year follow-up. The death of 77 patients (48%) was related to MRSA infection. In the univariate analysis (Table 2), predictors of MRSA-related death included septic shock at time of blood culture sampling (P < 0.01), APACHE II scores ≥ 15 (P < 0.01), rapidly fatal underlying disease (P = 0.049), malignancy (P < 0.01), neutropenia (P < 0.01), immunosuppressive therapy (P = 0.049), and age ≥ 60 years (P = 0.01). In contrast, non-fatal underlying condition was a protective factor against MRSA-related death (P = 0.02). Patients who were enrolled into the vancomycin loading trial had fewer MRSA-related deaths (6/21, 29%) than other patients treated with vancomycin (56/120, 47%), but the difference was not statistically significant (P = 0.24).

Effect of empirical glycopeptide therapy

The proportion of patients who died within 30 days in the empirical glycopeptide group was significantly higher than that in the non-empirical glycopeptide group (23/43, 53% versus 36/119, 30%, P = 0.01) (Table 3). After stratification by septic shock at time of blood culture sampling, which was more common in empirical glycopeptide group, there was no significant difference between the empirical glycopeptide and non-empirical glycopeptide groups in rates of MRSA-related death, all-cause 30 day mortality or length of hospitalization after onset of MRSA bacteraemia (Table 3). The 3 year Kaplan–Meier survival curves, stratified by septic shock at time of blood culture sampling, are shown in Figure 1. There was no significant difference between empirical glycopeptide and non-empirical glycopeptide groups (P = 0.31, septic shock group; P = 0.07, non-septic shock group).

In multivariate analysis for MRSA-related death and all-cause 30 day mortality (Table 4), a longer delay (measured in days) in the start of glycopeptide therapy was not a significant predictor of mortality after adjusting for the effects of other variables [adjusted odds ratio (OR) 0.99, 95% confidence interval (95% CI) 0.88–1.12, P = 0.92, adjusted hazard ratio 0.87, 95% CI 0.74–1.02, P = 0.08, respectively, Table 4]. In contrast, septic shock at time of blood culture, age ≥ 60 years and neutropenia were shown to be significant independent predictors of MRSA-related death or all-cause 30 day mortality (Table 4). Analysis for long-term outcome yielded three significant independent predictors for all-cause 1 year mortality: septic shock at time of blood culture (OR 14.2, 95% CI 1.5–131.0, P = 0.02), age ≥ 60 years (OR 5.6, 95% CI 2.3–46.9, P < 0.01) and malignancy (OR 7.3, 95% CI 1.4–27.5, P = 0.02). Non-fatal underlying condition was an independent protective factor (OR 0.42, 95% CI 0.18–0.99, P = 0.046). Age ≥ 60 years (OR 6.7, 95% CI 2.5–17.6, P < 0.01) was the only independent predictor for all-cause 3 year mortality. Non-fatal underlying condition was again an independent protective factor (OR 0.28, 95% CI 0.11–0.72, P < 0.01). A longer delay in the start of glycopeptide therapy was not a significant predictor of 1 or 3 year mortality after adjusting for the effects of other variables (adjusted OR 0.99, 95% CI 0.87–1.13, P = 0.90 and 0.96, 95% CI 0.84–1.10, P = 0.57, respectively).

Discussion

Our results did not support the hypothesis that earlier empirical use of glycopeptide therapy reduces mortality in patients

Table 2. Univariate analysis for risk factors of MRSA-related death

Variables	MRSA-related death		Rates ratio (95% CI)	*P* value
	Yes (*n* = 77) no. (%)	No (*n* = 85) no. (%)		
Empirical glycopeptide therapy	27 (35)	16 (19)	1.5 (1.1–2.0)	0.02*
Delay in start of therapy, days median (range)	2 (0–29)	3 (0–14)		0.02*
Initial vancomycin	62	79	1	
Initial teicoplanin	4	5	1.0 (0.3–3.6)	1.00
Age, years (mean ± SD)	66.7 ± 13.3	62.4 ± 17.7		0.22
Age ≥ 60 years	58 (75)	48 (56)	1.6 (1.1–2.4)	0.01*
Gender, male	45 (58)	56 (66)	0.8 (0.6–1.2)	0.30
Neutropenia (<500/mm^3)	11 (14)	2 (2)	1.9 (1.4–2.6)	<0.01*
Immunosuppressive therapy[a]	25 (32)	16 (19)	1.4 (1.0–2.0)	0.049*
Diabetes mellitus	26 (34)	19 (22)	1.3 (1.0–1.8)	0.12
Chronic heart disease[b]	23 (30)	19 (22)	1.2 (0.9–1.7)	0.29
Chronic lung disease[c]	10 (13)	10 (12)	1.1 (0.7–1.7)	0.82
Uraemia requiring dialysis	20 (26)	25 (29)	0.9 (0.6–1.3)	0.73
Decompensated liver cirrhosis[d]	13 (17)	7 (8)	1.4 (1.0–2.1)	0.15
Malignancies	34 (44)	12 (14)	2.0 (1.5–2.7)	<0.01*
McCabe classification				
Rapidly fatal	16 (21)	5 (6)	1.5 (1.1–2.1)	0.049*
Ultimately fatal	45 (58)	44 (52)	1	
Non-fatal	16 (21)	36 (42)	0.6 (0.4–1.0)	0.02*
APACHE II score[e]				
Median (range)	21 (5–37)	15 (1–31)		<0.01*
APACHE II score ≥15	63 (82)	48 (56)	2.1 (1.3–3.3)	<0.01*
Severity of SIRS[e]				
Septic shock	19 (25)	3 (4)	2.1 (1.6–2.8)	<0.01*
Severe sepsis	6 (8)	6 (7)	1.2 (0.7–2.3)	0.55
Sepsis	49 (64)	72 (85)	1	
No sepsis	3 (4)	4 (5)	1.1 (0.4–2.6)	1.00
Site of MRSA infection[f]				
Endocarditis	5 (6)	2 (2)	1.6 (0.9–2.9)	0.24
Pneumonia	18 (23)	10 (12)	1.4 (0.9–2.3)	0.14
Catheter-related infection	25 (32)	47 (55)	0.8 (0.5–1.3)	0.40
Urinary tract infection	3 (4)	2 (2)	1.4 (0.6–3.0)	0.65
Soft tissue infection	16 (21)	20 (24)	1	
Osteomyelitis	6 (8)	4 (5)	1.4 (0.7–2.5)	0.48
No obvious source	21 (27)	10 (12)	1.5 (1.0–2.4)	0.08

MRSA, methicillin-resistant *S. aureus*; CI, confidence interval; SIRS, systemic inflammatory response syndrome. Empirical glycopeptide group: patients began glycopeptide therapy before or within 48 h after blood culture sampling.
[a]Cytotoxic chemotherapy, corticosteroid or ciclosporin.
[b]Symptomatic coronary artery disease or congestive heart failure.
[c]Chronic obstructive pulmonary disease, bronchiectasis, or pneumoconiosis.
[d]With physical evidence of portal hypertension.
[e]At time of blood culture sampling.
[f]Some patients had more than one infected site.
*Statistically significant ($P < 0.05$).

with hospital-acquired MRSA bacteraemia. Kim *et al*.[16] also found no significant difference in MRSA-related mortality between patients who received an appropriate (30%, 9/30) and an inappropriate (39%, 38/97) empirical regimen ($P = 0.36$). Similarly, Roghmann[14] found no statistically significant difference in mortality from inappropriately empirically treated MRSA bacteraemia and mortality from appropriately empirically treated MSSA bacteraemia (relative risk 0.82, 95% CI 0.36–1.88) during a period of hospital policy restricting empirical vancomycin use. These results, however, should be interpreted with caution. Although ours, Kim's, and Roghmann's data did not support the existence of a beneficial effect of empirical glycopeptide therapy on patient outcomes, the same data did not refute it, either. Lack of significant difference between empirical glycopeptide group and non-empirical glycopeptide group implies an inconclusive result caused by the limited sample size, rather than no effect of empirical glycopeptide therapy.

Table 3. Effect of empirical glycopeptide therapy, stratified by septic shock at presentation

Outcome	Number of deaths (% of group)		*P* value
	Empirical glycopeptide group[a]	Non-empirical glycopeptide group	
All patients (n = 162)			
MRSA-related death	27/43 (63)	50/119 (42)	0.02**
All-cause mortality, 30-day	23/43 (53)	36/119 (30)	0.01**
Hospitalization days after onset of MRSA bacteraemia, median (range)	27 (3–224)	32 (1–353)	0.59
Patients had septic shock at time of blood culture sampling (n = 22)			
MRSA-related death	9/10 (90)	10/12 (83)	1.00
All-cause mortality, 30-day	9/10 (90)	10/12 (83)	1.00
Hospitalization days after onset of MRSA bacteraemia, median (range)	6.5 (3–160)	3 (1–353)	0.15
Patients without septic shock at time of blood culture sampling (n = 140)			
MRSA-related death	18/33 (55)	40/107 (37)	0.11
All-cause mortality, 30-day	14/33 (42)	26/107 (24)	0.05
Hospitalization days after onset of MRSA bacteraemia, median (range)	36 (1–224)	33 (3–309)	0.99

[a]Empirical glycopeptide group: patients began glycopeptide therapy before or within 48 h after blood culture sampling.
**Statistically significant ($P < 0.05$).

Table 4. Multivariate analysis for risk factors of MRSA-related death and 30-day all-cause mortality

Variables	MRSA-related death		All-cause 30-day mortality		All-cause 30-day mortality	
	Odds ratio[a]	*P* value	Odds ratio[a]	*P* value	Hazard ratio[b]	*P* value
Delay in start of therapy (daily increment)	0.99 (0.88–1.12)	0.92	0.83 (0.66–1.04)	0.10	0.87 (0.74–1.02)	0.08
Age ≥ 60 years	2.90 (1.25–6.75)	0.01*	2.13 (0.88–5.15)	0.09	1.49 (0.80–2.76)	0.21
Neutropenia (<500/mm^3)	3.87 (0.65–22.91)	0.14	4.44 (0.90–21.83)	0.07	3.15 (1.30–7.64)	0.01*
Malignancies	2.65 (0.92–7.60)	0.07	1.54 (0.52–4.60)	0.44	1.58 (0.78–3.20)	0.21
Immunosuppressive therapy	1.22 (0.45–3.32)	0.70	1.56 (0.55–4.39)	0.40	1.55 (0.73–3.29)	0.26
McCabe classification						
non-fatal	0.60 (0.25–1.41)	0.24	1.03 (0.40–2.64)	0.95	1.29 (0.64–2.61)	0.47
rapidly fatal	2.27 (0.54–9.63)	0.27	2.10 (0.52–8.47)	0.30	1.38 (0.59–3.23)	0.47
Septic shock at time of blood culture sampling	9.31 (2.35–36.8)	<0.01*	13.29 (3.50–50.6)	<0.01*	6.72 (3.62–12.5)	<0.01*

[a]Logistic regression analysis.
[b]Cox proportional hazard analysis.
*Statistically significant ($P < 0.05$).

An important limitation in previous studies[14,16] as well as ours is that the information was retrospectively obtained and therefore the measurement of time interval between blood culture sampling and the start of glycopeptide therapy allowed analysis only by days. Instead of days, a more appropriate evaluation should have been performed in hours. A delay of more than several hours could be critical in terms of influencing the outcomes of these patients.

Because observational studies, including the present one, cannot yield a conclusive result, it appears that placebo-controlled randomized clinical trials are indeed required to resolve this question. A small to moderate benefit of a therapeutic intervention usually requires randomized clinical trials to demonstrate this, because differences in patient characteristics between the groups in an observational study might bias results. The physicians had reasons to choose treatment, and these reasons are likely to influence outcomes. The reasons are not necessarily reflected in the variables we have gathered, and their influence is not necessarily completely corrected by multivariable analysis. Pre-defined inclusion criteria and adequate allocation concealment in a randomized clinical trial could indeed solve such issues. Before an evidence-based practice guideline can be formulated, a balanced view on this issue may be necessary. Use of institution-specific prediction models[27] for the probability of MRSA as the aetiology of hospital-acquired infections may help clinicians to decide whether to start glycopeptide antibiotics empirically. On the other hand, routine use of glycopeptide antibiotics as part of empirical therapy in patients with a low possibility of MRSA infection should be discouraged.

A meta-analysis of 14 randomized trials involving 2413 patients had shown no benefit of adding glycopeptides to initial empirical antimicrobial regimen for febrile neutropenic patients.[28] To be

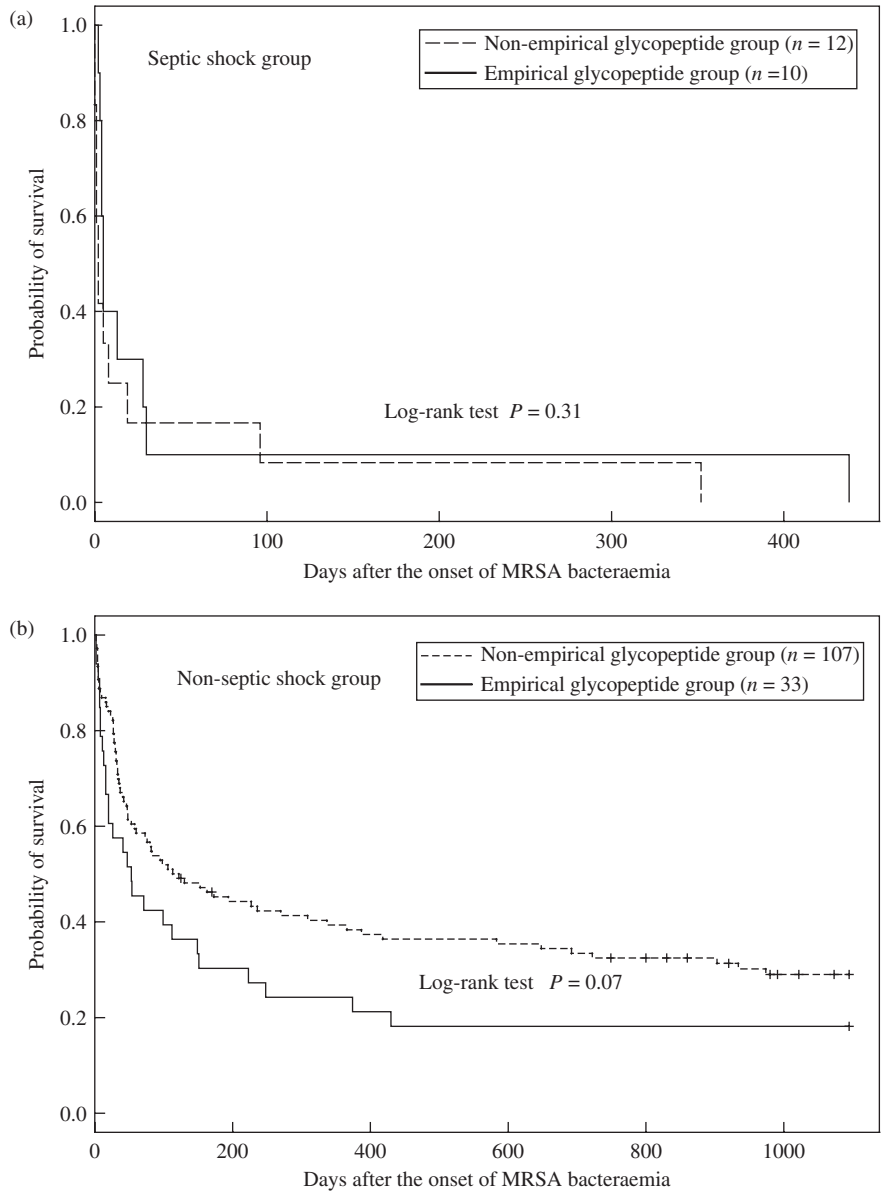

Figure 1. Kaplan–Meier survival curves of patients with MRSA bacteraemia, empirical glycopeptide therapy group versus non-empirical glycopeptide therapy group. The patients were further classified by: (a) presence of septic shock at the time of blood culture sampling; (b) no septic shock at the time of blood culture sampling.

life-saving in critically ill patients, empirically used agents must have a potent antimicrobial activity against the causal microorganism(s). Nevertheless, vancomycin has been consistently shown to be a much less effective antistaphylococcal drug than the semisynthetic penicillins in many *in vitro*, *in vivo* and clinical studies.[29–32] Failure to identify a statistically significant benefit of empirical glycopeptide therapy in our and Kim's studies, both involving only MRSA patients, may be explained by the unsatisfactory antimicrobial activity of vancomycin against MRSA.[29–32] In contrast, Lodise *et al*.[15] studied 103 patients with MRSA and 64 patients with MSSA, and they were able to identify a statistically significant beneficial effect (mortality 44.7% versus 86.7%, $P = 0.006$) of appropriate empirical therapy (either semisynthetic penicillins or vancomycin) among patients with APACHE II scores ≥ 15.5 and a high-risk source infection, but not in patients with lower risk.

The inferior efficacy of vancomycin against *S. aureus* can be further reduced by an elevation of MICs to 1–2 mg/L,[33] which is still well within the susceptibility range. A survey of MRSA strains at our hospital during 1995–1996 showed a vancomycin MIC_{50} of 0.5 mg/L and a MIC_{90} of 1 mg/L.[34] A second survey during 1998–1999 showed an increased vancomycin MIC_{50} of 1 mg/L and an increased MIC_{90} of 2 mg/L (see the Appendix).[35] This factor could be another reason that empirical glycopeptide therapy cannot be shown to be beneficial in our study.

For MRSA strains with an elevated vancomycin MIC, pharmacokinetic factors may potentially influence the efficacy of therapy. Glycopeptides have poor penetration into lung tissues.[36] Our patients with MRSA pneumonia did have a greater risk for mortality (Table 2), although this was not significant due to small sample sizes. Furthermore, standard vancomycin doses may

be subtherapeutic in critically ill patients during the first 24–48 h due to altered volume of distribution and other pharmacokinetic parameters in patients with sepsis syndrome.[37] This could also reduce the impact of earlier empirical vancomycin therapy for MRSA strains with a vancomycin MIC of 1–2 mg/L.

It should be acknowledged that culture sampling itself might have been delayed in some cases due to difficulties in suspecting the presence of MRSA bacteraemia. The timing of diagnosis and treatment might not be early enough even in the empirical glycopeptide group. We cannot rule out the possibility that aggressive treatment with a glycopeptide at an earlier stage of MRSA infections might be significantly beneficial. Efforts should be directed toward early recognition and rapid diagnosis of MRSA infections instead of merely relying on empirical glycopeptide therapy. Employment of more rapid molecular diagnostic methods such as *mecA* probes[38] may allow earlier treatment for MRSA infections after culture samples are drawn, and avoid unnecessary glycopeptides therapy for those do not have MRSA infections at the same time.

We conclude that the effect of earlier empirical use of glycopeptide therapy on reducing mortality in patients with hospital-acquired MRSA bacteraemia was not supported. Before we can confidently endorse a guideline supporting an aggressive approach with empirical glycopeptide use, randomized trials are required to provide solid evidence of its effectiveness in reduction of MRSA-related morbidity and mortality.

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Transparency declarations

None to declare. Dr Wen-Yi Shau is now an employee of GlaxoSmithKline.

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Appendix

Antimicrobial susceptibility of MRSA strains

By routine disc susceptibility test (Table 5), all of the MRSA strains isolated from included patients were susceptible to both vancomycin and teicoplanin. Two (1%) strains were also susceptible to erythromycin, clindamycin, minocycline and trimethoprim/sulfamethoxazole. Another four (2%) strains were resistant to macrolides but susceptible to clindamycin, minocycline and trimethoprim/sulfamethoxazole. Among the remaining 156 strains, 80 (49%) were resistant to all four tested non-β-lactam, non-glycopeptide antibiotics: erythromycin, clindamycin, minocycline and trimethoprim/sulfamethoxazole. The other strains were resistant to at least two of the above four agents.

Table 5. Routine disc susceptibility of MRSA strains involved in this study

	Susceptible no. (%) (n = 162)
Vancomycin	162 (100)
Teicoplanin	162 (100)
Erythromycin	3 (2)
Clindamycin	25 (15)
Minocycline	62 (38)
Trimethoprim/sulfamethoxazole	33 (20)

Routine screening using brain–heart infusion agar supplemented with vancomycin 4 mg/L did not detect any vancomycin-intermediate *S. aureus* strain. To survey the level of MICs of vancomycin to the MRSA strains isolated from patients involved in this study, we randomly selected 18 strains from the available 102 blood culture isolates and conducted MIC determination using the standard agar dilution method (National Committee for Clinical Laboratory Standards. *Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically-Fourth Edition: Approved Standard M7-A4*. NCCLS, Wayne, PA, USA, 1997). Among the 18 tested MRSA isolates, the vancomycin MICs were 1 mg/L in 16 strains and 0.5 mg/L in two strains.