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Impact of Initial Vancomycin Trough Concentration on Clinical and Microbiological Outcomes of Methicillin-Resistant *Staphylococcus aureus* Bacteremia in Children

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It is important to use vancomycin in a proper manner to ensure optimal drug exposure. Despite extensive use of vancomycin in children, studies on its optimal trough concentration (C_{trough}) in the pediatric population remained rare. This retrospective study included children < 18 years old with culture-confirmed methicillin-resistant *Staphylococcus aureus* (MRSA) bacteremia who were hospitalized in our institute from January 2010 to April 2014. Clinical characteristics, initial vancomycin dose, C_{trough} and clinical/microbiological outcomes were retrospectively collected from medical records. Forty-six MRSA bacteremia cases occurring to the patients with a mean age of 22.0 ± 46.9 months were included and all of them were healthcare-associated. Severe diseases requiring intensive care unit (ICU) stay, mechanical ventilation and/or resulting in death were observed in 57.8% (26/45); all-cause 30-day fatality was 11.1% (5/45). An initial C_{trough} ≥ 15 μg/mL was achieved in only 4 (8.7%) cases with an average vancomycin dosage of 40.6 ± 7.9 mg/kg/day. Persistent bacteremia at 48 hours after initiation of vancomycin was observed more frequently in children with initial C_{trough} < 10 μg/mL than in those with C_{trough} ≥ 10 μg/mL (P = 0.032). However, there was no statistically significant difference between the two groups in terms of 30-day mortality and recurrent bacteremia (P = 0.899, and P = 0.754, respectively). Although initial C_{trough} may be a useful parameter for minimizing early microbiological failure, it does not predict 30-day fatality or recurrence in pediatric MRSA bacteremia. Further prospective data on vancomycin dosing are needed to find the optimal drug exposure and clarify its impact on clinical outcomes in pediatric populations.

Keywords: MRSA Bacteremia; Vancomycin Concentration; Children; Korea

INTRODUCTION

Vancomycin is a glycopeptide antimicrobial with an important therapeutic role in treating invasive methicillin-resistant *Staphylococcus aureus* (MRSA) infection in children in community-associated (CA) and healthcare-associated (HA) settings (1). Because of the significant burden of MRSA infection in hospitals and the community, it is important to use vancomycin appropriately to ensure optimal drug exposure. Though some authors question the usefulness of therapeutic drug monitoring (TDM) of vancomycin and warn of unnecessary hospital costs, appropriate TDM is acknowledged as the most powerful method of adjusting vancomycin use in MRSA bacteremia (2). Studies of the pharmacokinetics and pharmacodynamics (PK/PD) of vancomycin have advocated that a ratio of the area under the curve to the minimum inhibitory concentration (AUC/MIC) of ≥ 400 is optimal for achieving clinical effectiveness in adults (3). This is frequently complemented by a recommended serum vancomycin C_{trough} of > 15 μg/mL when the MIC is 1 μg/mL; to avoid the emergence of resistance, it should at least be maintained above 10 μg/mL (4). However, these recommendations are mainly based on guidelines supported by adult data and may not extrapolate to young children.

Despite extensive use of vancomycin in children, information about the optimal regimen to achieve PK/PD targets in the pediatric population remains limited (5). Recent PK/PD studies suggest that routine aggressive dosing may be unnecessary in pediatric invasive MRSA infections, because a C_{trough} of 7–10 μg/mL at a dose of 15 mg/kg every 6 hours predicted achievement of AUC/MIC > 400 in > 90% of children infected by MRSA with MIC ≤ 1 μg/mL (6). In addition, the relationship between the C_{trough} and AUC in neonates is similar to those in children regardless of gestational age and kidney function (7). Therefore, higher trough concentrations of 15 to 20 μg/mL are likely to be unnecessary in children and neonates based on AUC/MIC considerations (6,7). Meanwhile vancomycin treatment failure in

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MRSA bacteremia is most common in premature infants and immunocompromised individuals, even though vancomycin trough serum concentrations ≥ 15 μg/mL are achieved (8).

The aims of this study were to determine whether initial C_{trough} could be used as a practical parameter for predicting clinical and microbiological outcomes with the cut-off value at 10 μg/mL, which is the minimum level avoiding the emergence of hetero-resistant vancomycin-intermediate *S. aureus* (4), and anticipating achievement of AUC/MIC > 400 in pediatric MRSA infection by pharmacokinetic modeling (6,7).

MATERIALS AND METHODS

Study populations

This retrospective study was conducted at Asan Medical Center Children's Hospital, which is a 252 bed university-affiliated tertiary hospital located in Seoul, Korea; it has a pediatric intensive care unit (PICU), neonatal intensive care unit (NICU), hematology/oncology ward, surgical ward, and general pediatric wards.

Children aged under 18 years with culture-confirmed MRSA bacteremia, who were hospitalized in our institute during the study period from January 2010 to April 2014, were eligible for enrollment. Other focal infections without bloodstream infection were not included. Patients were included only if they received vancomycin for at least 48 hours and their initial C_{trough} had been checked within ≤ 96 hours of start of treatment. Corresponding clinical data including demographic profiles, diagnoses, primary sites of infection, underlying diseases, durations of hospital stay, intensive care unit (ICU) stays, need for mechanical ventilation, and HA risk factors were abstracted retrospectively from electronic medical records. Only the first MRSA isolate detected during a single clinical episode occurring within a 4-week period was included in the analysis, and duplicates from the same patient were excluded. Patients were included regardless of their underlying medical conditions such as congenital heart diseases, genetic/metabolic diseases, hemato-oncological diseases, chronic lung diseases, and neurological disorders. However, patients on renal replacement therapy such as hemodialysis, or neonates admitted to the nursery or NICU were excluded.

Initial dosages of vancomycin (mg/kg/day), which was determined by the reference of '*Pediatric and Neonatal Dosage Handbook*' (9), and the resulting serum vancomycin concentration data were collected. The first trough sample before the 4th or 5th dose was obtained within 30 minutes prior to the next dose of vancomycin.

Definitions

Fever was defined as any temperature ≥ 38.0°C. The primary focus of infection was defined as the culture-positive site and/or a clinically evident site of infection concomitant with bacteremia, and central line-associated blood stream infection (CLABSI) was defined according to the Centers for Disease Control and Prevention (CDC) guidelines (10). Recurrent MRSA bacteremia was defined as MRSA regrowth on blood cultures after at least one culture-negative month (11). Co-infection was defined as the isolation of an organism in addition to MRSA from the same initial blood culture, or clinical or laboratory evidence of viral infection at the time of isolation of MRSA.

Strain identification and antimicrobial susceptibility testing

Isolates were identified and the antimicrobial susceptibilities of the *S. aureus* isolates were decided using a MicroScan WalkAway 96-Combo Pos 28 panels (Siemens, West Sacramento, CA, USA). This machine contained six vancomycin wells with concentrations ranging from 0.5 to 16.0 μg/mL and the maximum MIC value within the range was selected to determine MIC_{50} and MIC_{90}. Antimicrobial susceptibility testing data included 8 antibiotics; gentamycin, ciprofloxacin, trimethoprim/sulfamethoxazole, rifampin, tetracyclin, clindamycin, linezolid, and vancomycin. MRSA isolate of intermediate resistance or full resistance were defined as resistant. The in vitro macrolide-lincosamide-streptogramin $_B$ (MLS_B)-inducible phenotype was detected by the D-zone test (double-disk diffusion test). Multidrug-resistance (MDR) was defined as acquired non-susceptibility to at least one agent in each of three or more antimicrobial categories (12).

Clinical/microbiological outcomes

To evaluate the clinical and microbiological outcomes according to C_{trough} level, the children with MRSA bacteremia were divided into those with initial vancomycin C_{trough} < 10 μg/mL and ≥ 10 μg/mL, respectively. As measures of clinical outcome we included resolution of fever after 48 hours of vancomycin use, recurrent MRSA bacteremia, and 30-day all-cause fatality. To evaluate microbiological outcomes, we compared time to negative conversion of blood culture and presence of persistent bacteremia at 48–72 hours of vancomycin administration.

Statistical analysis

While continuous variables were compared using the independent *t*-tests or analysis of variance (ANOVA), the χ^2 test or Fisher's exact test were used for categorical variables. Risk factors for 30-day mortality or persistent bacteremia at 48 hours were investigated by logistic regression analysis. *P* values were 2-sided and considered significant at $P < 0.05$ using SPSS 18.0 (SPSS Inc., Chicago, IL, USA).

Ethics statement

This study was approved by the Institutional Review Board of

Asan Medical Center with a waiver of informed consent for retrospective, de-identified data collection and analysis (IRB No. 2014-0300).

RESULTS

Patient characteristics

During the study period from January 2010 to April 2014, a total of 61 cases of MRSA bacteremia occurred in our institute among individuals < 18 years old. Of these, 15 were excluded for the following reasons; 12 patients required hemodialysis or NICU stay, 2 in whom vancomycin C_{trough} was not monitored, and one treated with teicoplanin. Finally, 46 episodes of MRSA bacteremia were included in the analysis and the demographic and clinical characteristics of the patients are shown in Table 1. Mean age of patients was 22.0 ± 46.9 months (range, 0–17 years old) and 82.6% (38 out of 46) were aged under 24 months; 54.3% (25 of 46) were male. All were HA MRSA cases and occurred in children with underlying medical conditions, the majority with congenital heart disease. Of the cases, 41.3% were primary MRSA bacteremia while the others involved definite focal infections including CLABSI (41.3%, 19/46), pneumonia (15.2%, 7/46), ventriculoperitoneal shunt infection (4.3%, 2/46) and surgical site infection (4.3%, 2/46); none of them were bone and joint infections or skin and soft tissue infections. Fever was the most frequent initial symptom (34/46, 73.9%) and 16 (34.8%) patients presented with unstable vital signs including hypotension, bradycardia and respiratory difficulty. However, non-specific find-

Table 1. Characteristics of children with MRSA bacteremia according to the initial vancomycin trough concentration (C_{trough})

Characteristics	C_{trough} < 10 μg/mL (n = 35)	C_{trough} ≥ 10 μg/mL (n = 11)	Total (n = 46)	*P* value*
Mean age ± SD, mon	26.6 ± 52.9	7.3 ± 8.3	22.0 ± 46.9	0.045
Sex of male, No. (%)	19 (54.3)	6 (54.5)	25 (54.3)	0.988
Hospital stay before onset of the MRSA bacteremia ± SD, day	17.2 ± 37.9	106.5 ± 179.0	38.5 ± 94.6	0.005
Underlying disease				
Congenital heart disease	15 (42.9)	6 (54.5)	21 (45.7)	0.497
Malignancy	3 (8.6)	1 (9.1)	4 (8.7)	0.957
Chronic liver disease	1 (2.9)	0 (0.0)	1 (2.2)	0.571
Congenital anomaly/genetic disorders	3 (8.6)	0 (0.0)	3 (6.5)	0.315
Chronic lung disease	8 (22.9)	3 (37.3)	11 (23.9)	0.765
Neurologic diseases	3 (8.6)	0 (0.0)	3 (6.5)	0.315
Others†	10 (28.6)	3 (27.3)	13 (28.3)	0.933
Presence of co-infection‡	1 (2.9)	2 (18.2)	3 (6.5)	0.138
Presence of an invasive device§	26 (74.3)	11 (100.0)	37 (80.4)	0.061
Initial clinical symptom				
Presence of fever (≥ 38.0°C)	27 (77.1)	7 (63.6)	34 (73.9)	0.374
Unstable vital signs‖	8 (22.9)	8 (72.7)	16 (34.8)	0.002
ICU stay	16/35 (45.7)	9/10 (90.0)	25/45 (55.6)	0.013
Need for mechanical ventilation	15/35 (42.9)	8/10 (80.0)	23/45 (51.1)	0.038
Initial laboratory finding				
WBC in peripheral blood, /μL	16,022 ± 9,492	20,018 ± 13,241	16,978 ± 10,488	0.275
Serum CRP, mg/dL	7.5 ± 10.9	5.5 ± 5.7	7.0 ± 9.9	0.553
Serum BUN, mg/dL	12.1 ± 7.6	16.8 ± 5.5	13.3 ± 7.4	0.080
Serum creatinine, mg/dL	0.3 ± 0.1	0.4 ± 0.3	0.3 ± 0.2	0.073
Primary focus of MRSA bacteremia				
None	13 (37.1)	6 (54.5)	19 (41.3)	0.307
CLABSI	15 (42.9)	4 (36.4)	19 (41.3)	0.703
Pneumonia	6 (17.1)	1 (9.1)	7 (15.2)	0.517
Others¶	4 (11.4)	0 (0.0)	4 (8.7)	0.241
Removal of primary focus	6 (17.1)	1 (9.1)	7 (15.2)	0.517
Simultaneous use of other antibiotics, No. (%)	28 (80.0)	9 (81.8)	39 (84.8)	0.895
Mean ± SD of initial vancomycin dose, mg/kg/day	41.0 ± 8.1	39.4 ± 7.6	40.6 ± 7.9	0.536
Mean ± SD of initial C_{trough}, μg/mL	5.6 ± 2.0	15.6 ± 5.8	8.0 ± 5.4	< 0.001

MRSA = methicillin-resistant *Staphylococcus aureus*, SD = standard deviation, ICU = intensive care unit, WBC = white blood cell, CRP = C-reactive protein, BUN = blood urea nitrogen, CLABSI, central line-associated blood stream infection.

*In each indicated age group, continuous variables were compared using the independent t-test. Binominal variables were compared using the χ^2 test; †Others includes surgical conditions such as congenital diaphragmatic hernia, congenital megacolon, hypospadias, jejunal atresia, tracheoesophageal fistula, omphalocele and other endocrine disease such as hypothyroidism, and pseudohypoaldoteronism; ‡Co-infections included respiratory viral infections such as rhinovirus (n = 2) and adenovirus (n = 1); §Invasive devices included vascular catheters (n = 26), tracheostomy (n = 3), gastrostomy (n = 3), ventriculoperitoneal shunt (n = 2), and colonostomy (n = 1); ‖Unstable vital signs means any of the signs of bradycardia, respiratory difficulty, and hypotension, or requirement of vasopressor; ¶Others includes ventriculo-peritoneal shunt infections (n = 2) and superficial surgical site infections (n = 2).

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ings such as vomiting or nausea were observed as an initial symptom in 5 (10.9%) patients, and 1 (2.2%) patient had no clinical symptoms other than a finding of elevated C-reactive protein (CRP). Mean duration of fever to initial positive culture was 1.9 ± 2.4 days.

Clinical manifestations according to vancomycin C_{trough}

Initial average dose of vancomycin was 40.6 ± 7.9 mg/kg/day (range, 21.4–63.1 mg/kg/day). The initial C_{trough} was 8.0 ± 5.4 μg/mL (range, 2.3–25.6 μg/mL), and only 4 (8.7%) patients achieved the C_{trough} ≥ 15 μg/mL. Numbers (%) of children according to range of initial C_{trough} were as follows; C_{trough} < 5 μg/mL, 14 (30.4%), ≥ 5 μg/mL to < 10 μg/mL, 21 (45.7%), and ≥ 10 μg/mL to < 15 μg/mL, 7 (15.2%).

The patients belonging to the group with initial C_{trough} < 10 μg/mL were older (26.6 ± 52.9 months vs. 7.3 ± 8.3 months ; P = 0.045), had a shorter hospital stay prior to MRSA bacteremia (17.2 ± 37.9 days vs. 106.5 ± 179.0 days; P = 0.005) and showed relatively milder clinical courses ; initial presentation with unstable vital signs, ICU stay and requirement for mechanical ventilation were less frequent in the group with C_{trough} < 10 μg/mL (22.9% vs. 72.7%, P = 0.002; 45.7% vs. 90.0%, P = 0.013; 42.9% vs. 80.0%, P = 0.038, respectively) (Table 1). However, no significant differences were observed between the groups with initial vancomycin C_{trough} < 10 μg/mL and ≥ 10 μg/mL, in the other aspects including presence of underlying disease, primary focus of infection and whether the primary focus was removed or not.

Clinical and microbiological outcomes

Clinical outcomes associated with MRSA bacteremia were analyzed in only 45 cases because one patient was transferred to a care hospital within 14 days from the onset of MRSA bacteremia (Table 2). Severe diseases requiring ICU stay, mechanical ventilation and/or resulting in death were observed in 57.8% (26/45); all-cause 30-day fatality was 11.1% (5/45) with average duration from onset of MRSA bacteremia to death of 11.8 days (range, 2–20 days). Nephrotoxicity defined as an increase in serum creatinine of 0.5 mg/dL from baseline occurred in one patient with initial C_{trough} of 6.6 μg/mL; none of the 4 children with high vancomycin troughs of > 15 μg/mL developed nephrotoxicity.

As follow-up blood culture at 48–72 hours was missed in some cases, 36 of the 46 cases could be included in the analysis of initial microbiological outcomes at 48–72 hours of vancomycin administration; persistent bacteremia at 48–72 hours was observed in 63.9% (23/36) of these patients (Table 2). Average time to negative conversion for the first time was 5.3 ± 4.5 days. MRSA bacteremia recurred in 7 (15.2%) patients after at least one culture-negative month; 3 were CLABSI and 4 had primary bacteremia without a definite focus. All of the recurrent CLABSI cases had a history of salvage therapy without removal of the infected central venous catheter. Mean recurrence interval was 80 days (range, 28–260 days).

Impact of vancomycin C_{trough} on clinical and microbiological outcomes

There was no statistically significant difference between the two groups with initial vancomycin C_{trough} < 10 μg/mL and ≥ 10 μg/mL, in terms of clinical outcome including 30-day mortality and recurrence (P = 0.899, and P = 0.754, respectively) (Table 2). However, persistent bacteremia at 48 hours was observed more frequently in the group with initial C_{trough} < 10 μg/mL (77.8%, compared to 33.3%; P = 0.032), and these patients had a tendency to require longer time for negative conversion (5.3 days, compared to 3.5 days; P = 0.236). Although univariate logistic regression analysis suggested initial C_{trough} < 10 μg/mL was associated with persistent bacteremia at 48 hours (odds ratio [OR], 7.00; 95% confidence interval [CI], 1.02–47.97), multivariate logistic regression analysis could not identify statistically significant predictors for persistent bacteremia at 48–72 hours and 30-

Table 2. Clinical and microbiological outcomes of children with MRSA bacteremia according to initial vancomycin trough concentration (C_{trough}) and vancomcyin MIC

Characteristics	Initial C_{trough}, μg/mL			Vancomycin MIC, μg/mL			
	C_{trough} < 10 (n = 35)	C_{trough} ≥ 10 (n = 11)	P value*	MIC < 1.0 (n = 12)	MIC = 1.0 (n = 27)	MIC > 1.0 (n = 7)	P value*
Microbiologic outcome†							
Time to negative conversion, day	5.3 ± 4.5	3.5 ± 2.5	0.236	6.1 ± 6.5	4.1 ± 2.8	5.7 ± 4.0	0.350
Persistent bacteremia at 48 hr	21/27 (77.8)	2/6 (33.3)	0.032	6/9 (66.7)	12/19 (63.2)	5/5 (100.0)	0.273
Persistent bacteremia at 72 hr	18/31 (58.1)	2/5 (40.0)	0.451	5/9 (55.6)	10/21 (47.6)	5/6 (83.3)	0.300
Clinical outcome							
Recurrent MRSA infection‡	5/35 (14.3)	2/11 (18.2)	0.754	3/12 (25.0)	2/27 (7.4)	2/7 (28.6)	0.209
Resolution of fever at 48 hr§	11/27 (40.7)	3/7 (42.9)	0.919	7/11 (63.6)	9/18 (50.0)	4/5 (80.0)	0.447
All-cause fatality within 30 day‖	4/35 (11.4)	1/10 (10.0)	0.899	3/12 (25.0)	2/26 (7.7)	0/7 (0.0)	0.171

MRSA = methicillin-resistant *Staphylococcus aureus*, MIC = minimum inhibitory concentration.

*Continuous variables were compared by the independent *t*-tests or analysis of variance (ANOVA), and the χ^2 test or Fisher's exact test were used for categorical variables; †Microbiological outcome analysis was done in the available cases because follow-up blood cultures within 72 hours were missed in some cases; ‡Recurrent MRSA infection was defined as MRSA regrowth after at least one month of culture-negativity; §Because some cases presented without fever at the onset of MRSA bacteremia, only febrile cases are included; ‖One patient, who was transferred to care hospital within 14 days from the onset of MRSA bacteremia, could not be included in this analysis.

Table 3. Risk factors for persistent bacteremia and 30-day fatality in pediatric MRSA bacteremia

Variables	Persistent bacteremia at 48 hours		30-day all-cause fatality	
	Unadjusted*	Adjusted†	Unadjusted*	Adjusted†
Mean age	1.01 (0.99–1.03)	1.00 (0.98–1.03)	1.01 (0.99–1.02)	1.01 (0.99–1.01)
Hospital day before the onset of the MRSA bacteremia	0.99 (0.98–1.00)	1.00 (0.98–1.01)	1.00 (1.00–1.01)	1.00 (0.99–1.01)
Presentation with unstable vital signs	0.65 (0.12–3.47)	2.00 (0.14–28.02)	3.50 (0.52–23.70)	6.06 (0.39–95.24)
ICU stay	0.73 (0.16–3.28)	1.55 (0.06–39.70)	3.62 (0.37–35.29)	1.76 (0.12–25.68)
Need for mechanical ventilation	0.77 (0.17–3.41)	1.29 (0.05–31.40)	Not applicable‡	Not applicable‡
Initial C_{trough}	0.91 (0.77–1.07)	1.15 (0.83–1.58)	0.96 (0.78–1.18)	0.98 (0.69–1.40)
Initial C_{trough} < 10 μg/mL	7.00 (1.02–47.97)	33.81 (0.22–5,174.94)	1.16 (0.11–11.74)	2.68 (0.01–524.77)

Values are presented as odds ratio (95% confidence interval).
MRSA = methicillin-resistant *Staphylococcus aureus*, ICU = intensive care unit.
*Univariate logistic regression analysis was carried out including the factors that were significantly different depending on initial C_{trough} as presented in Table 1; †Multivariate logistic regression was done adjusting for the any risk factors included in the univariate analysis; ‡All of the fatal cases required mechanical ventilation.

day fatality (Table 3).

In a subgroup analysis of children aged under 24 months, which included 82.6% (38/46) of the study population, 73.7% (28/38) had an initial C_{trough} < 10 μg/mL; all-cause 30-day fatality was 8.1% (3/37). Persistent bacteremia at 48 hours was observed more frequently when initial C_{trough} was below 10 μg/mL (78.3%, compared to 33.3% in the group with C_{trough} ≥ 10 μg/mL; P = 0.034).

Antimicrobial susceptibilities

Among the 46 MRSA isolates, the multi-drug resistance rate was 46.9% and 69.6% were resistant to erythromycin. With an erythromycin-inducible clindamycin resistance rate of 88.9% (8/9), the overall rate of resistance to clindamycin was 52.2% (24/46). Frequencies of resistance to trimethoprim/sulfamethoxazole and rifampin were 2.2% (1/46) and 4.3% (2/46), respectively. The vancomycin MIC_{50} and MIC_{90} were 1.0 and 2.0 μg/mL, respectively. MRSA isolates with vancomycin MIC < 1.0 μg/mL, 1.0 μg/mL, and > 1.0 μg/mL comprised 26.1% (12/46), 58.7% (27/46), and 15.2% (7/46), respectively, and no MRSA isolates with vancomcyin MIC > 2.0 μg/mL were detected.

The clinical and microbiological outcomes of the children with MRSA bacteremia according to the vancomycin MIC are shown in Table 2, however, vancomycin MIC did not significantly influence clinical and microbiologic outcomes of MRSA bacteremia in this study.

DISCUSSION

Our findings suggest that initial C_{trough} < 10 μg/mL could be used as a predictor of microbiological failure at 48 hours of vancomycin therapy for children with MRSA bacteremia, even though multivariate logistic regression analysis could not identify statistical significance. However, initial C_{trough} < 10 μg/mL did not significantly influence 30-day mortality or recurrence even when we adjusted for clinical status at presentation. This may be partly due to the better clinical outcomes in pediatric MRSA bacteremia than in adult cases. Indeed, overall 30-day mortality associated with MRSA bacteremia was 11.1% in this study, which was much lower than that in adult patients (13). A recent prospective cohort study reported a 25.6%, 30-day mortality of invasive MRSA infections in a Korean population with median age 64 years (14). It may be pointless to monitor initial vancomycin C_{trough} to optimize final clinical outcomes in pediatric MRSA bacteremia, in which, compared to adult cases, relatively favorable outcomes can be expected regardless of initial vancomycin C_{trough}.

The AUC of vancomycin is a well-known theoretical PK/PD model reflecting the effectiveness of vancomycin exposure (15). Because it is nearly impossible to measure an accurate AUC in clinical practice especially in young children, it is important to develop an appropriate PK/PD model. In our study, more than 80% of our study population was less than 24 months old and no very appropriate model for calculating AUC was available in this age group; estimation of an AUC using vancomycin clearance and creatinine clearance based on the model developed by Frymoyer et al. (16), was originally developed to predict vancomycin AUC_{24}/MIC in children aged 2 to 12 years. Although a Bayesian model employing the serum creatinine value and one set of trough and peak vancomycin concentrations has been developed to estimate a PK model for vancomycin in young children (17,18), our study was conducted retrospectively and the standard of care in our institute involves checking only trough levels during vancomycin therapy.

There is controversy regarding the association of vancomycin MIC and clinical outcomes, in some reports higher vancomycin MIC value had a higher likelihood of treatment failure (19) in others not (20,21). In this study, vancomycin MIC did not impact on the clinical and microbiologic outcomes of MRSA bacteremia in young children.

This study had some limitations. First, it was retrospective and included a relatively small number of patients and about one-fourth of the cases of MRSA bacteremia could not be included in the initial microbiological outcome analysis because of missing follow-up blood cultures within 72 hours, even though it is recommended that follow-up blood cultures should be con-

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ducted every 48 to 72 hours until a negative result is obtained in our institute. Second, during the study period from January 2010 to April 2014, the initial dose of vancomycin was usually 40 mg/kg/day—with some exceptions such as central nervous system (CNS) infections where a starting dose of 60 mg/kg/day was used based on the *Pediatric and Neonatal Dosage Handbook* (9)—even though this is suboptimal according to the recent recommendation of a daily dose of 60 mg/kg in children. Since 2012–2013, however, the recommended initial dose of vancomycin was increased from 40 mg/kg/day to 60 mg/kg/day with further modification according to the TDM report in cases of invasive MRSA infection regardless of CNS or non CNS infection. Vancomycin is a well-known age-dependent pharmacokinetic antibiotic, because creatinine clearance has a crucial role in vancomycin pharmacodynamics and the vancomycin clearance of children is 2 or 3 times higher than that of adults (14,19). As a consequence, it was hard to obtain the adult target range in most children with the dosage of 40 mg/kg/day. Thirdly, the paucity of appropriate models for calculating AUCs given only the serum trough values of vancomycin in younger children under 2 years old made it difficult to determine whether the PK/PD parameters were comparable to the data obtained in older population groups. However, there have been few clinical studies to determine the impact of the vancomycin C_{trough} and MIC on clinical and microbiological outcomes in MRSA bacteremia among young children < 2 years old, and the only available literature being theoretical PK/PD models predicting clinical outcomes in pediatric MRSA infections (6,22).

In conclusion, initial C_{trough} may be a useful TDM parameter in pediatric MRSA bacteremia for reducing early microbiological failure, though it did not impact on final clinical outcomes including 30-day fatality. Further prospective data on vancomycin dosing are needed to find the optimal drug exposure and clarify its impact on clinical outcomes in pediatric populations.

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DISCLOSURE

The authors have no potential conflicts of interest to disclose.

AUTHOR CONTRIBUTION

Study concept and design: Lee J. Data acquisition: Yoo RN, Kim SH. Analysis and interpretation of the data: Yoo RN, Kim SH, Lee J. Writing and revision: Yoo RN, Lee J. Final approval of manuscript submission: all authors.

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