Journal of Microbiology, Immunology and Infection (2017) 50, 494–499

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ORIGINAL ARTICLE

Vancomycin dosing and target attainment in children

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Received 30 April 2015; received in revised form 31 August 2015; accepted 31 August 2015
Available online 18 September 2015

KEYWORDS
area under curve;
children;
trough concentration;
vancomycin

Abstract *Background/Purpose:* The aim of this study is to determine the best dosing strategy for vancomycin by studying the associated factors and examining correlations between the area under the plasma concentration-time curve (AUC) values and trough concentrations in children.
Methods: Children aged 3 months to 18 years were included if they received vancomycin for more than three doses between January 1, 2010 and December 31, 2012 and had one or more serum vancomycin trough concentrations. Vancomycin clearance (CL) was calculated using the following model: $CL = 0.248*Wt^{0.75}*(0.48/\text{serum creatinine})^{0.361}*[\ln(\text{age})/7.8]^{0.995}$. The AUC (mg-h/L) was calculated by 24-hour dose (mg/kg/d)/CL(L/h). The value of AUC divided by the minimum inhibitory concentration (MIC) of vancomycin was AUC/MIC.
Results: A total of 218 children were included. The mean age was 6.0 ± 5.1 years and the mean body weight was 20 ± 11.7 kg. Vancomycin trough concentrations were moderately correlated with AUC values ($r^2 = 0.232$, $p < 0.01$). Dosing of 15 mg/kg/dose q6h produced significantly higher AUC values ($p < 0.001$) and vancomycin trough concentrations ($p < 0.001$) compared to dosing of 10 mg/kg/dose q6h. In children receiving a 10-mg/kg/dose q6h, 5.6% (5/90) achieved the target trough concentrations of 15–20 μg/mL and 9.5% (5/90) achieved the goal AUC/MIC ≥ 400. In children receiving a 15-mg/kg/dose q6h, 13% (6/46) achieved the target trough concentrations of 15–20 μg/mL, whereas 54.3% (25/46) achieved the goal AUC/MIC ≥ 400.
Conclusion: A 15-mg/kg/dose q6h compared to a 10-mg/kg/dose q6h is more likely to achieve target trough concentrations of 15–20 μg/mL and the goal AUC/MIC ≥ 400.

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http://dx.doi.org/10.1016/j.jmii.2015.08.027

Introduction

Vancomycin is a glycopeptide antibiotic that inhibits bacterial cell wall synthesis, and is used in the treatment of infections caused by Gram-positive bacteria such as *Streptococci*, *Staphylococci*, and *Enterococcus* species.[1] It was first used in 1952 and lost favor due to the introduction of methicillin in 1958. However, due to the emergence of methicillin-resistant *Staphylococcus aureus* (MRSA) worldwide, the use of vancomycin returned. In Taiwan, MRSA was first documented in the early 1980s and rapidly increased in the 1990s.[2] A significant trend of a decrease in the incidence of hospital-acquired MRSA was noted in the past 11 years.[3] However, community-acquired MRSA infections have been increasingly reported in pediatric patients since 2000. To date, the rate of methicillin resistance amongst community-acquired MRSA isolates from pediatric patients is >50%.[4] Vancomycin is still the drug of choice for invasive MRSA infections.[5] As expected, vancomycin will be used more frequently when treating pediatric patients hospitalized for serious staphylococcal infections due to the increase of prevalence. Vancomycin exhibits time-dependent bactericidal effects when the serum concentration is three to four times the minimum inhibitory concentration (MIC) of the organism.[6] The increase of antimicrobial resistance in MRSA urges higher dosing of vancomycin to achieve higher serum concentrations. In adults, vancomycin area under the plasma concentration-time curve (AUC) to MIC ratio (AUC/MIC) $\geq$ 400 best predicts clinical and bacteriological outcomes for patients with severe infections caused by MRSA.[7] In MRSA bacteremia, a low initial vancomycin AUC/MIC is an independent risk factor for vancomycin treatment failure.[8] Study has shown that in adults, a vancomycin trough concentration of 15–20 μg/mL correlates with the AUC/MIC $\geq$ 400 goal.[9] Measuring AUC/MIC by traditional methods is not practical in a clinical setting because it requires multiple serum vancomycin concentration measurements. Vancomycin trough concentrations have remained the most commonly used parameter. In 2011, the Infectious Diseases Society of America released a guideline for the treatment of MRSA infections. The guideline recommended vancomycin 15 mg/kg/dose q6h in treating children with serious or invasive disease and aimed for concentrations of 15–20 μg/mL in children.[5] However, studies have shown that these target trough concentrations of 15–20 μg/mL are rarely achieved in children and Le et al[10] proposed that AUC/MIC $\geq$ 400 is a more realistic target.

There is as yet no study regarding the target attainment of vancomycin dosing in Taiwan. Here, we provide the vancomycin pharmacological data of Taiwanese children, and determine the target attainment of vancomycin treatment for invasive MRSA infection by the current dosing strategy.

Methods

Inclusion criteria

This retrospectively analyzed cohort study was conducted in a single medical center, the Mackay Memorial Hospital, Taipei, Taiwan. Children aged 3 months to 18 years were included if they received vancomycin for more than three doses between January 1, 2010 and December 31, 2012, and had one or more serum vancomycin trough concentrations.

Data collection

Drug concentrations were routinely monitored in all children receiving vancomycin. Dose adjustments were performed based on drug concentrations. Trough concentrations were obtained 30 minutes before the fourth vancomycin dose. Creatinine levels were also monitored routinely. Medical records of children with vancomycin trough concentrations measured were retrospectively reviewed. Data including sex, age, weight, serum creatinine, vancomycin dosage, and vancomycin trough concentrations were collected. MIC data of MRSA isolates in pediatric participants receiving vancomycin in our hospital from January 1, 2010 to June 30, 2014 was also collected.

Exclusion criteria

Children aged <3 months were excluded due to the difficulty of creatinine clearance calculation and AUC estimation. Children receiving hemodialysis, peritoneal dialysis, and continuous venovenous hemofiltration were excluded.

Data analysis

Vancomycin clearance (CL) was calculated using a model designed by Le et al[10]: $CL = 0.248*Wt^{0.75}*(0.48/\text{serum creatinine})^{0.361}*[\ln(\text{age})/7.8]^{0.995}$. Then, AUC (mg-h/L) was calculated by 24-hour dose (mg/kg/d)/CL (L/h). The vancomycin trough concentrations were categorized into <5 μg/mL, 5–10 μg/mL, 10–15 μg/mL, 15–20 μg/mL, and >20 μg/mL. The vancomycin AUC was categorized into <200 mg-hr/L, 201–400 mg-hr/L, 401–600 mg-hr/L, and ≥600 mg-hr/L. We also calculated the AUC/MIC level according to the common vancomycin MIC value to MRSA. The target attainment of AUC/MIC is ≥400. The initial dosing of vancomycin was categorized into seven groups: Group 1: 10 mg/kg/dose q6h, Group 2: 15 mg/kg/dose q6h, Group 3: 15 mg/kg/dose q8h, Group 4: 15 mg/kg/dose q12h, Group 5: 20 mg/kg/dose q6h, Group 6: 10 mg/kg/dose q12h, and other. The target attainment of different dosing groups was compared to the recommended vancomycin 15 mg/kg/dose q6h in treating children.

Statistical analyses

Descriptive analyses were performed to characterize the demographic and clinical data of children using statistical software (SPSS, version 15.0; SPSS Science, Chicago, IL, USA).

Relations of AUC (mg-hr/L), daily dose (mg/kg/d), and trough concentrations (μg/mL) were analyzed by Pearson's correlation test. Student *t* test or one-way analysis of variance was used to compare the value of AUC/MIC and trough concentrations between groups of vancomycin dosing and daily dose. All tests were two-tailed at the level of significance of $p = 0.05$.

Results

A total of 475 children were screened; 253 children < 3 months old were excluded. Four children aged 3 months to 18 years were excluded due to receiving hemodialysis, peritoneal dialysis, and continuous venovenous hemofiltration. The remaining 218 children were included in the study. The mean age was 5.97 years and mean body weight was 20 kg. The categorized dosing of vancomycin, AUC, and the vancomycin trough concentrations are listed in Table 1. The correlations between trough concentrations, daily dose, and AUC are shown in Figure 1. The vancomycin trough concentration is moderately correlated with daily dose (mg/kg/d; $r^2 = 0.112$, $p < 0.001$), AUC is strongly correlated with daily dose (mg/kg/d; $r^2 = 0.619$, $p < 0.01$), and trough concentration is moderately correlated with AUC ($r^2 = 0.232$, $p < 0.01$).

Among all children, 21.6% (47/218) reached the goal of AUC/MIC ≥ 400, and 7.8% reached the target trough concentrations of 15–20 μg/mL. When MIC = 0.5 μg/mL, 89% of children achieved AUC/MIC ≥ 400. When MIC = 1 μg/mL, 21.6% of children achieved AUC/MIC ≥ 400. When MIC = 2 μg/mL 1.4% of children achieved AUC/MIC ≥ 400 (Figure 2A).

We also did comparisons between groups with distinct daily doses without consideration of dose interval, which showed that a higher daily dose has significantly higher AUC

Table 1 Demographic data of study group.

Character	Mean	Standard deviation
Age (y)	6.0	5.7
Body weight (kg)	20.0	17.1
Creatinine level (mg/dL)	0.39	0.28
Dosing (mg/kg/d)	43.7	16.8
	No.	%
Female sex	111	50.9
Dosage		
10 mg q6h	90	41.3
15 mg q6h	46	21.1
15 mg q12h	22	10.1
10 mg q12h	15	6.9
20 mg q6h	7	3.2
15 mg q8h	7	3.2
Other	31	14.2
Trough (μg/mL)		
≤5	48	22.0
6–10	88	40.4
11–15	37	17.0
16–20	17	7.8
>20	15	6.9
AUC (mg-hr/L)		
≤200	22	10.0
200–300	84	38.5
300–400	65	29.8
400–500	20	9.2
500–600	12	5.5
>600	15	6.9

AUC = area under the plasma concentration-time curve.

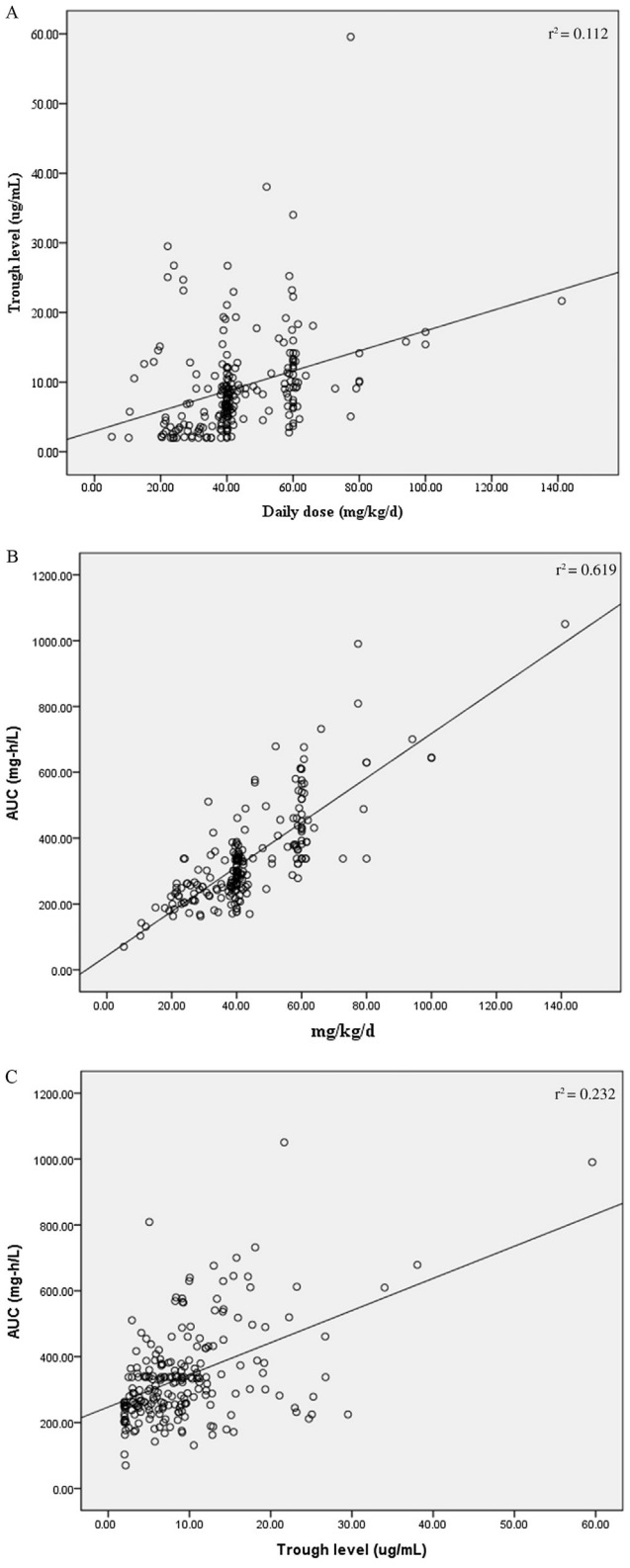

Figure 1. Correlations between trough concentrations, daily dose, and AUC. (A) Correlation of trough concentrations and daily dose; (B) correlation of AUC and daily dose; and (C) correlation of trough concentrations and AUC.

and vancomycin trough levels (Table 2). The target attainments of different daily doses are shown in Figure 2B.

There were 30 MRSA isolates in pediatric patients receiving vancomycin in our hospital from January 1, 2010 to June 30, 2014. A total of 22/30 (66.7%) of MRSA isolates had a vancomycin MIC $\leq$ 0.5 μg/mL, 6/30 (20.0%) had a vancomycin MIC $\leq$ 1 μg/mL, and 2/30 (6.7%) had a vancomycin MIC = 2 μg/mL. No vancomycin intermediate *Staphylococcus aureus* or vancomycin resistant *S. aureus* were found.

When comparisons were made between Group 1 (10 mg/kg/dose q6h) and Group 2 (15 mg/kg q6h), Group 2 had significantly higher AUC values ($p < 0.001$) and vancomycin trough concentrations ($p < 0.001$). In Group 1, only 5.6% (5/90) of children achieved the target trough range of 15–20 μg/mL, whereas 9.5% (5/90) achieved the goal AUC/MIC $\geq$ 400 when the MIC = 1 μg/mL, and 90% (81/90) achieved the goal AUC/MIC $\geq$ 400 when the MIC = 0.5 μg/mL; no children achieved the goal AUC/MIC $\geq$ 400 when the MIC = 2 μg/mL. In Group 2, only 13% (6/46) of children achieved the target trough range of 15–20 μg/mL, whereas 54.3% (25/46) achieved the AUC/MIC $\geq$ 400 when MIC = 1 μg/mL, and 100% (46/46) achieved the goal AUC/MIC $\geq$ 400 when MIC = 0.5 μg/mL; no children achieved the goal AUC/MIC $\geq$ 400 when the MIC = 2 μg/mL (Figure 2C).

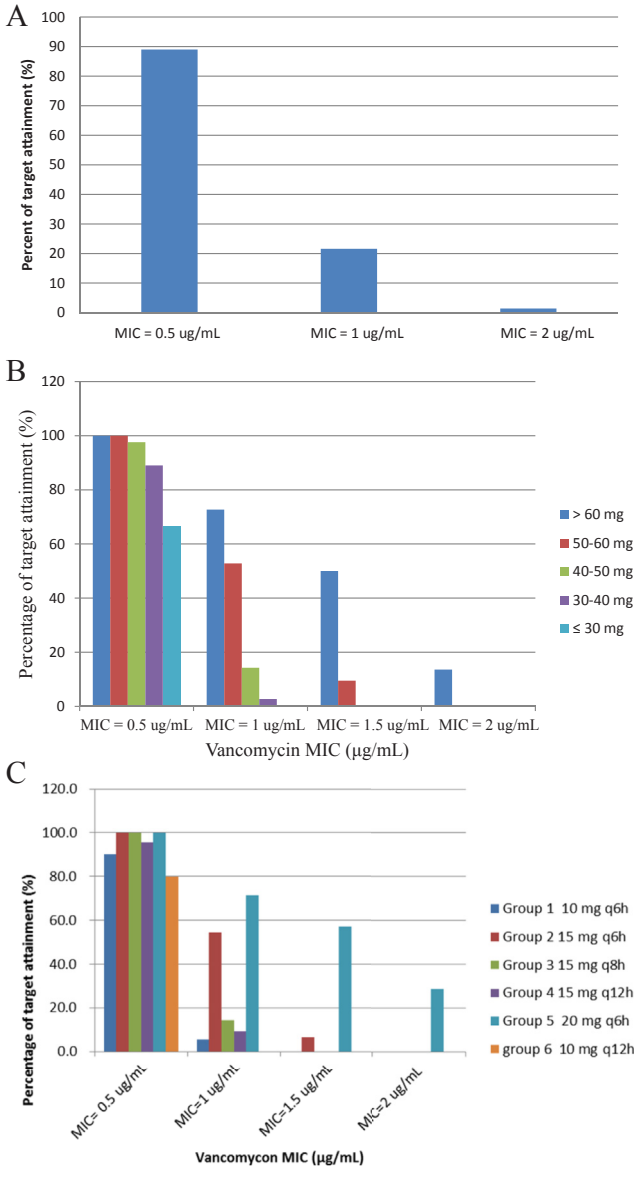

Figure 2. AUC/MIC target attainment. (A) AUC/MIC target attainment in all participants; (B) AUC/MIC target attainment of different daily dose of vancomycin; and (C) AUC/MIC $\geq$ 400 target attainment of different vancomycin dosing group. AUC = area under the plasma concentration-time curve; MIC = minimum inhibitory concentration.

Discussion

Due to the high prevalence of MRSA in Taiwan,[11,12] vancomycin is usually used as the empirical therapy if patients are suspected of having serious MRSA infections such as bacteremia or necrotizing pneumonia, or if other antimicrobials like oxacillin or penicillin were not effective. In larger studies, Eiland et al[13] reviewed trough vancomycin concentrations of 438 participants, when the dosing was 15 mg/kg/dose q6h and showed that only 49% reached therapeutic trough concentrations (>10 μg/mL). Our study showed similar results, with only 54.3% (25/46) of children dosed with 15 mg/kg/dose q6h reaching the trough concentrations of >10 μg/mL. Another study, by Frymoyer et al,[14] showed that with a dosing regimen of 15 mg/kg/dose q6h, only 14% of participants achieved initial trough concentrations in the range 15–20 μg/mL. Similar to our study, only 13% (6/46) of participants who received a dosing regimen of 15 mg/kg/dose q6h achieved vancomycin trough concentrations of 15–20 μg/mL.

We found that most children do not achieve vancomycin trough concentrations of 15–20 μg/mL even under high dosing. Having known the fact that the target trough is not an optimal target,[15] AUC was surveyed as a target for pediatric vancomycin dosing. Our study showed that only 9.5% of children achieved AUC $\geq$ 400 mg-hr/L by receiving the 10 mg/kg/dose q6h and 54.3% of children achieved AUC $\geq$ 400 mg-hr/L by receiving the 15 mg/kg/dose q6h. Similar results were found in a study by Chhim et al,[16] which showed that only 17% and 40% of participants achieved AUC $\geq$ 400 mg-hr/L when receiving 40 mg/kg/d and 60 mg/kg/d, respectively. It is also important to determine the MIC of the organism being treated. When MIC = 0.5 μg/mL, > 90% of participants receiving the 10 mg/kg/dose q6h and the 15 mg/kg/dose q6h achieved AUC/MIC $\geq$ 400. This suggests that a higher dosing strategy may not be needed with MIC = 0.5 μg/mL. When MIC = 1 μg/mL, only 54.3% of participants receiving 15 mg/kg/dose q6h achieved AUC/MIC $\geq$ 400 and only 13% of participants achieved the target trough of 15–20 μg/mL. With an MIC = 2 μg/mL, no case achieved AUC/MIC $\geq$ 400. Although vancomycin is still the recommended first line therapy with an MIC of $\geq$2 μg/mL, alternative drugs such as daptomycin, tigecycline, or linezolid should be considered.

We found that the predicted AUC correlated with trough concentrations. Our study showed that trough concentrations of 10–15 μg/mL correlate with AUC = 400 mg-hr/L. The study which provided the equation for AUC for our

Table 2 The AUC level and trough level by actual daily dose.

	Daily dose (mg/kg)	Patient no.	Mean	SD	*p*
AUC (mg-hr/L)					<0.001
	>60	22	579.5	202.6	
	50–60	42	436.0	100.9	
	40–50	42	325.4	90.2	
	30–40	73	279.9	63.8	
	≤30	39	216.9	555.7	
Trough level (μg/mL)					<0.001
	>60	39	14.1	11.1	
	50–60	25	12.2	7.6	
	40–50	42	9.2	4.9	
	30–40	73	7.0	4.3	
	≤30	39	7.7	8.0	

AUC = area under the plasma concentration-time curve; SD = standard deviation.

study also showed that AUC of 400 mg-hr/L correlated to a mean C_{min} of approximately 8–9 μg/mL.[10] One study using pharmacokinetic modeling by Frymoyer et al[17] also showed a good correlation between AUC and trough concentration. However, Chhim et al[16] found that AUC had a poor correlation with trough concentration. In a previous study, Alford et al[18] also found that glomerular filtration rate equations do not accurately predict vancomycin trough concentrations in pediatric patients.

Due to the creep of vancomycin MIC of MRSA, the use of an aggressive dosing strategy for treatment is necessary. In adults, a review study found that higher trough levels (>15 μg/mL) were associated with twofold increased odds of nephrotoxicity relative to lower troughs of <15 μg/mL.[19] In children, whether higher troughs lead to an increase in vancomycin-induced nephrotoxicity is still in debate. One recent study showed that maintaining trough concentrations >15 μg/mL is not associated with an increased rate of nephrotoxicity in a Paediatric Intensive Care Unit (PICU) population.[20] No documented renal toxicity was noted in our study participants. Based on our study, if we aim for achieving higher trough concentrations, higher vancomycin doses must be used and we will need to monitor the renal function under the concern of increasing potential of nephrotoxicity.

The limitations to our study include the small number of patients sampled and the retrospective nature. In some patients with complicated underlying conditions such as prematurity and profound edema, blood sampling is very difficult. The condition also made it hard to determine the actual body weight for vancomycin dosing. Rapid changes of renal function also made the doctor need to adjust the vancomycin dosing frequently in these patients. Due to the difficulty in blood sampling, a portion of vancomycin trough concentrations was not measured in the correct timing.

In conclusion, the predicted AUC correlated with trough concentrations and vancomycin dosing. Vancomycin dosing regimens of 15 mg/kg q6h had better achievement of the target trough concentrations of 15–20 μg/mL and predicted AUC/MIC ≥ 400 in most patients. If the vancomycin MIC is 0.5 μg/mL, the 15-mg/kg/dose q6h can achieve the goal of AUC/MIC > 400 in all patients. We suggest the dose of empiric vancomycin is 15 mg/kg/dose q6h during the treatment of children with severe MRSA infections.

Conflicts of interest

All contributing authors declare no conflicts of interest.

References

1. Schilling A, Neuner E, Rehm SJ. Vancomycin: a 50-something-year-old antibiotic we still don't understand. *Cleve Clin J Med* 2011;**78**:465–71.
2. Chen ML, Chang SC, Pan HJ, Hsueh PR, Yang LS, Ho SW, et al. Longitudinal analysis of methicillin-resistant *Staphylococcus aureus* isolates at a teaching hospital in Taiwan. *J Formos Med Assoc* 1999;**98**:426–32.
3. Lai CC, Chu CC, Cheng A, Huang YT, Hsueh PR. Correlation between antimicrobial consumption and incidence of health-care-associated infections due to methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant enterococci at a university hospital in Taiwan from 2000 to 2010. *J Microbiol Immunol Infect* 2013;**48**:431–6.
4. Huang YC, Chen CJ. Community-associated meticillin-resistant *Staphylococcus aureus* in children in Taiwan, 2000s. *Int J Antimicrob Agents* 2011;**38**:2–8.
5. Liu C, Bayer A, Cosgrove SE, Daum RS, Fridkin SK, Gorwitz RJ, et al. Clinical practice guidelines by the infectious diseases society of America for the treatment of methicillin-resistant *Staphylococcus aureus* infections in adults and children. *Clin Infect Dis* 2011;**52**:e18–55.
6. Foster JK, Lentino JR, Strodtman R, DiVincenzo C. Comparison of in vitro activity of quinolone antibiotics and vancomycin against gentamicin- and methicillin-resistant *Staphylococcus aureus* by time-kill kinetic studies. *Antimicrob Agents Chemother* 1986;**30**:823–7.
7. Moise-Broder PA, Forrest A, Birmingham MC, Schentag JJ. Pharmacodynamics of vancomycin and other antimicrobials in patients with *Staphylococcus aureus* lower respiratory tract infections. *Clin Pharmacokinet* 2004;**43**:925–42.
8. Jung Y, Song KH, Cho J, Kim HS, Kim NH, Kim TS, et al. Area under the concentration-time curve to minimum inhibitory concentration ratio as a predictor of vancomycin treatment outcome in methicillin-resistant *Staphylococcus aureus* bacteraemia. *Int J Antimicrob Agents* 2014;**43**:9–83.
9. Rybak MJ, Lomaestro BM, Rotschafer JC, Moellering RC, Craig WA, Billeter M, et al. Vancomycin therapeutic guidelines: a summary of consensus recommendations from the infectious diseases Society of America, the American Society of Health-

System Pharmacists, and the Society of Infectious Diseases Pharmacists. *Clin Infect Dis* 2009;**49**:325—7.
10. Le J, Bradley JS, Murray W, Romanowski GL, Tran TT, Nguyen N, et al. Improved vancomycin dosing in children using area under the curve exposure. *Pediatr Infect Dis J* 2013;**32**: e155—63.
11. Chuang YY, Huang YC. Molecular epidemiology of community-associated meticillin-resistant *Staphylococcus aureus* in Asia. *Lancet Infect Dis* 2013;**13**:698—708.
12. Lu CY, Ting YT, Huang LM. Severe *Streptococcus pneumoniae* 19A pneumonia with empyema in children vaccinated with pneumococcal conjugate vaccines. *J Formos Med Assoc* 2014; **114**:783—4.
13. Eiland LS, English TM, Eiland 3rd EH. Assessment of vancomycin dosing and subsequent serum concentrations in pediatric patients. *Ann Pharmacother* 2011;**45**:582—9.
14. Frymoyer A, Guglielmo BJ, Wilson SD, Scarpace SB, Benet LZ, Hersh AL. Impact of a hospitalwide increase in empiric pediatric vancomycin dosing on initial trough concentrations. *Pharmacotherapy* 2011;**31**:871—6.
15. Gordon CL, Thompson C, Carapetis JR, Turnidge J, Kilburn C, Currie BJ. Trough concentrations of vancomycin: adult therapeutic targets are not appropriate for children. *Pediatr Infect Dis J* 2012;**31**:1269—71.
16. Chhim RF, Arnold SR, Lee KR. Vancomycin dosing practices, trough concentrations, and predicted area under the curve in children with suspected invasive staphylococcal infections. *J Pediatric Infect Dis Soc* 2012;**2**:259—62.
17. Frymoyer A, Guglielmo BJ, Hersh AL. Desired vancomycin trough serum concentration for treating invasive methicillin-resistant Staphylococcal infections. *Pediatr Infect Dis J* 2013; **32**:1077—9.
18. Alford EL, Chhim RF, Crill CM, Hastings MC, Ault BH, Shelton CM. Glomerular filtration rate equations do not accurately predict vancomycin trough concentrations in pediatric patients. *Ann Pharmacother* 2014;**48**:691—6.
19. van Hal SJ, Paterson DL, Lodise TP. Systematic review and meta-analysis of vancomycin-induced nephrotoxicity associated with dosing schedules that maintain troughs between 15 and 20 milligrams per liter. *Antimicrob Agents Chemother* 2013;**57**:734—44.
20. Cies JJ, Shankar V. Nephrotoxicity in patients with vancomycin trough concentrations of 15—20 mug/ml in a pediatric intensive care unit. *Pharmacotherapy* 2013;**33**:392—400.