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Optimization of an empiric vancomycin dosing algorithm for improved target concentration attainment in patients with thermal injury

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ABSTRACT

Objective: Vancomycin empirical dosing studies in thermally injured patients have netted low successful target attainment and most excluded renal dysfunction, limiting applicability. In a previous study, the authors performed a retrospective analysis of 124 patients' measured pharmacokinetic parameters to calculate optimal dose and interval for intermittent infusion regimens and find predictors of clearance and total daily dose. The objective of this study was to improve the accuracy of attaining goal therapeutic targets with initial vancomycin regimens in patients with thermal injury through retrospective modeling.

Methods: In this phase 2 study, variables collected and calculated regimens in phase 1 were utilized to try and create an improved empiric vancomycin dosing algorithm in patients with thermal injury. Logistic regression was utilized to determine best predictors of dosing vancomycin every 6 and 8 h. The strongest models were built as individual algorithms and tested for accuracy of target attainment. Each algorithm produced a regimen for each patient that was then tested utilizing each patient's actual measured pharmacokinetic parameters.

Results: Univariable logistic regression of 41 variables identified 27 and 23 to be predictive of dosing every 8 or 6 h, respectively. The most predictive multivariable model for dosing every

Abbreviations: ABA, American Burn Association; AKIN, Acute Kidney Injury Network; AUC_{24}, 24-hour area under the curve; AUC_{24}:MIC, area under the curve to minimum inhibitory concentration ratio; BMI, body mass index; CG, Cockcroft-Gault; CL, clearance; CrCl, creatinine clearance; C_{max}, true peak; C_{min}, true trough; CVVH, continuous venovenous hemofiltration; DSI, days since injury; IBW, ideal body weight; k_e, elimination rate constant; LRTS, Likelihood ratio test statistic; MIC, minimum inhibitory concentration; SCr, serum creatinine; TBSA, total body surface area; Vd, volume of distribution.

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8 h consisted of creatinine clearance (CrCl) ≥ 80 ml/min, Acute Kidney Injury Network classification <1, and total body surface area burned ≥ 10 percent. For dosing every 6 h, CrCl ≥ 80 ml/min, age ≤ 40 years old, days since injury ≤ 6, and serum creatinine (SCr) ≤ 0.8 were most predictive. Based on the top 5 multivariable models for each dosing interval, 7 algorithms were built to produce recommended regimens. The highest performing algorithm resulted in trough concentrations of <10 mg/L (23%), 10–20 mg/L (65%), 15–20 mg/L (26%), and >20 mg/L (11%); area under the concentration curve (AUC) > 400 mg hr/L (83%); and AUC > 400 mg hr/L without having a trough >20 mg/L (72%).

Conclusions: The algorithm that resulted in the highest target attainment without overdosing recommended 15 mg/kg dosed every 24 h for CrCl ≥ 30, every 12 h for CrCl 31–79, every 8 h for patients with CrCl ≥ 80 ml/min, and every 6 h only if the patient with a CrCl ≥ 80 ml/min is also ≤ 40 years old and has a SCr ≤ 0.8. Caution is warranted for groups underrepresented in this study, such as those with very low CrCl, a low BMI, or receiving renal replacement therapy. This algorithm should be validated in other centers for patients with thermal injuries.

1. Introduction

Thermal injury invokes a hypermetabolic response in patients that affects many physiological processes, including drug metabolism [1,2]. Many studies have demonstrated the augmented dosing recommendations of several medications in patients with thermal injury, secondary to increased clearances (CL) and variable volumes of distribution (Vd) [3–8]. Vancomycin pharmacokinetics have been demonstrated significantly different in patients with thermal versus non-thermal injuries and even that of others critically injured [9–12]. Even when considering only thermally injured patients, predicting individual pharmacokinetics remains difficult, secondary to significant inter-patient variability [13]. This variably has been partially explained by the effects seen by different volumes of distribution between patient or burn center and percent total body surface area burned (TBSA) [10,11,14]. Variability is also seen within each patient. Significant intra-patient variability can also owe to varying volumes of distribution throughout the patient's stay and timing of initiation with regard to days since injury (DSI) [13,14].

Current guidance recommends maintaining a steady state trough concentration of greater than 10 mg/L to minimize failure and emergence of resistance [15]. While a goal of 15–20 mg/L is recommended for severe infections, such as bacteremia, pneumonia, and meningitis, some argue attaining troughs above 15 mg/L is unnecessary to ensure efficacy and may increase risk for vancomycin-induced nephrotoxicity [15–17]. Isolated wound infections and cellulitis may only benefit from a target of 10–15 mg/L, however caution is advised in patients presenting with systemic symptoms. Patients presenting with thermal injury add further complexity to the definition of severe infection, as many traditional sepsis symptoms are persistently positive through the entire stay regardless of infection [18–20]. Temperatures over 39°C, heart rates above 120 beats per minute, minute ventilations above 12 L/min, elevated white blood cell counts, and hyperglycemia with insulin resistance are not uncommon and make for difficult differentiation of a severe infection from the burn itself [18–21]. The trough recommendation of 15–20 mg/L is supported by little outcome based evidence, but accounts for limited penetration for some sites of infection and also established breakpoints for the most commonly treated Gram positive pathogens. Growing evidence continues to suggest steady state trough concentrations may not be the optimum target and that focus should be shifted toward area under the curve to minimum inhibitory concentration ratio (AUC_{24}:MIC) [22,23]. AUC_{24}:MIC targets ranging from greater than 345 all the way up to 866 have been proposed to be ideal and depend on outcome measured, site of infection, and minimum inhibitory concentration (MIC) of the targeted pathogen [21,23,24]

To date, various models have been proposed and simulations performed to improve empiric dosing algorithms in thermally injured patients. Accuracy of initial regimens have thus far resulted in target attainment of only about twenty percent in patients with thermal injury [13,25]. Previously, the authors performed a retrospective analysis of 124 thermally injured patients to determine dosing recommendations for achieving aggressive troughs of 15–20 mg/L [14]. The phase 1 study was conducted to find variables that contribute to the altered pharmacokinetics frequently seen in thermally injured patients receiving vancomycin. An average of 55.2 mg/kg/day was required in the entire cohort, while 64.7 mg/day (16.2 mg/kg every 6 h) was required in the patients without renal dysfunction. Days since injury (DSI), percent TBSA, and Cockcroft-Gault (CG) estimated creatinine clearance (CrCl) predicted faster clearances and need for higher doses. The purpose of the current phase 2 study was to utilize the patient specific regimens calculated in phase 1 to build a dosing algorithm that would best incorporate the complexity of the thermally injured patient and result in the most accurate empiric dosing regimens for thermally injured patients with severe infections.

2. Methods

2.1. *Patient population*

This study was a part of a retrospective cohort study conducted at a single burn center. The study was approved by both the

hospital and university Institutional Review Boards. The phase 1 study included patients admitted October 20, 2012–November 30, 2015 who received intravenous vancomycin for any indications. Patients were excluded if they were under eighteen years of age, admitted for any reason other than thermal or inhalation injury, vancomycin initiated within forty-eight hours of injury, or lacked 2 paired post-distribution concentrations. Patients were also excluded if vancomycin concentrations were unrecorded, unreliable, or obtained prior to steady state [14]. The phase 2 study included the final 124 patient cohort of the phase 1 study.

2.2. Data collection

All data was collected during the phase 1 study. Briefly, all initial dosing methods were accepted and no patient was excluded based on chosen empiric dosing regimen. Demographic data was collected utilizing the institutional electronic medical record. Using the data collected, the elimination rate constant (k_e), true peak (C_{max}), true trough (C_{min}), half-life, Vd, CL, 24-h area under the curve (AUC_{24}), and predicted dose required to obtain target concentrations were calculated as previously described [14]. CrCl was calculated as an estimate via the Cockcroft-Gault equation utilizing ideal body weight (IBW).

2.3. Phase 1 pharmacokinetic analysis [14]

During Phase 1, calculations were performed using a one-compartment model. Half-life was calculated as $[0.693/k_e]$. The elimination rate constant (k_e) was calculated as $[\ln (C_1/C_2)/(t_2 - t_1)]$, where $(t_2 - t_1)$ represents the time between the two concentrations. C_{max} was $[C_1/e^{-ke^*t}]$, where t represents the amount of time after the end of infusion the concentration was drawn. C_{min} was $[C_2{}^*e^{-ke^*t}]$, where t represents the amount of time remaining in the interval from when the concentration was drawn. Vd was calculated as $[D/(k_e{}^*T)]^*[(1-e^{-ke^*T})/(C_{max} - (C_{min}{}^*e^{-ke^*T})]$, where D is the dose and T is the infusion time. AUC_{24} was calculated as $[D_{24}/(k_e{}^*Vd)]$, where D_{24} is the total dose in mg given during a 24-h period. CL was calculated as $[K_e{}^*Vd]$. Predicted interval (τ) was calculated as $[\ln (40/17.5)/k_e + T]$ and rounded to the nearest clinically feasible interval. Predicted dose was calculated as $[40^*k_e{}^*Vd^*T^*(1-e^{-ke^*\tau})/(1-e^{-ke^*T})]$ and rounded to the nearest 250 mg. The calculations performed in this study are identical to actual bedside practice at the authors' institution for all patients with a possible severe infection. Utilizing 40 and 17.5 mg/L for the target concentrations in the predicted equations allowed flexibility during rounding of each interval and dose for the trough to stay within the desired therapeutic range of 15–20 mg/L. Because of rounding, the final regimen for each patient would not actual target 17.5 mg/L, but fall near 15 mg/L. The new rounded predicted dose and interval were then mathematically validated, based on a predicted C_{min} goal of 15–20 mg/L. Predicted C_{min} was calculated as [predicted $C_{max}{}^*e^{-ke^*(\tau - T)}$], where predicted C_{max} was calculated as $[D/(k_e{}^*Vd^*T)]^*[(1-e^{-ke^*T})/(1-e^{-ke^*\tau})]$. Creatinine clearance was calculated according to the CG equation [26]. For authenticity, serum creatinine was not rounded and calculations resulting in augmented clearances were not truncated.

2.4. Phase 2 statistical analysis

Statistical analysis was done using Sigma Plot 11.2. Logistic regression was utilized for univariable and multivariable analysis in attempts to find variables with potential to independently predict need for vancomycin dosing at least every 8 h and also at least every 6 h. Based on observations from Phase 1 data, analyzing when to empirically initiate patients on every 8 or 6 h intervals appeared to be a potential target for improvement. Variables collected during Phase 1 were subjected to logistic regression (Appendix A Table A1). The regimens utilized during regression analysis were the calculated regimens from Phase 1 required to achieve a goal trough of 15–20 mg/L, as described above. Variables found to be significant ($p < 0.05$) during univariable analysis were subject to multivariable regression to find predictive models of best fit. Model fit was determined by the Likelihood ratio test (LRTS). The statistically strongest models, as determined by LRTS, were then incorporated into separate dosing algorithms and analyzed for performance. Performance was compared utilizing descriptive statistics and odds ratios.

2.5. Phase 2 algorithm evaluation

The primary objective of this study was to build an algorithm with as few variables as possible that would improve current empiric dosing practices. Inclusion of too many variables would results in overfitting and likely excessive underdosing, as fewer patients would meet criteria for dosing every 8 or 6 h. Overfitting would also damage external validity, allowing less flexibility for error if significant variables were mistakenly missed. Too few variables would result in an unacceptably high rate of exceeding the goal therapeutic range. The number or algorithms built was not planned a priori, but decided after seeing the results from the regression analysis. Actual prescribed regimens for the large cohort of 124 patients studied in Phase 1 demonstrated target attainment parallel to present literature and a focus for potential improvement (42% were <10 mg/L, 48% 10–20 mg/L, 22% 15–20 mg/L, 10% >20 mg/L, 74% AUC ≥ 400 mg hr/L, and 65% AUC ≥ 400 mg hr/L without overdosing) [14]. Each algorithm was built utilizing variables identified during statistical analysis with a series of "IF" statements in Microsoft Excel 2013 to determine suggested interval. For suggested maintenance dose, both 15 and 18 mg/kg actual body weight were tested in separate algorithms, utilizing "MROUND" for rounding to nearest 250 mg and a maximum of 2500 mg per dose. Utilizing the suggested regimen for each algorithm and actual patient pharmacokinetic profiles (k_e and Vd) determined during Phase 1, predicted regimens for each patient and each algorithm were calculated as referenced above. Phase 1 observed troughs and AUCs for each patient were utilized as comparators to each algorithm's estimated troughs and AUCs.

3. Results

One-hundred and twenty-four patients' pharmacokinetic profiles were utilized during data analysis. Patient age, TBSA burned, and CrCl ranged from 18 to 84 years old, 0.1 to

79 percent, and 8 to 230 ml/min, respectively. Fifty-six percent had vancomycin initiated for a suspected invasive wound infection, 12% for culture positive bacteremia, 10% for pneumonia, 2% for cellulitis, and 20% had a different or unknown source. Sixty-five patients had cultures that grew *Staphylococcus spp*, 10 with *Enterococcus spp*, 3 with *Streptococcus spp*, and 52 patients had other pathogens or final cultures without significant bacterial growth. Predicted regimens required to obtain trough values of 15–20 mg/L were calculated for each patient. Table 1 lists demographics divided by predicted dosing interval. Patients with the most frequent dosing of vancomycin (every 4 or 6 h vs 8 h vs 12 h) were more likely to be younger and initiated on the antimicrobial closer to their date of injury. Age was subjected to further quantile analysis in attempt to better identify a threshold to apply to the empiric dosing algorithm. Age remained significantly different all the way down to younger than 25 years of age. Most of the age significance was explained by differences in the every 4 or 6 h vs the 12 h grouping.

Forty-one variables were subjected to univariable analysis via logistic regression to find the strongest predictors of patients that would benefit from dosing at least every 8 h. Twenty-seven variables significantly predicted need for dosing at least every 8 h (Appendix B Table B1). During decile analysis, several of the CrCl, age, and SCr thresholds were significant. Similarly, many of the DSI values were found significant. Significant variables were subjected to analysis by multivariable logistic regression. Table 2 lists the highest-performing multivariable models for dosing every 8 h. While TBSA ≥ 10 was not significant during univariable regression analysis, it was included in multivariable modeling based on Phase 1 results for potential to improve the final model.

A similar approach was taken for analysis of patients that underwent dosing at least every 6 h. Twenty-three variables significantly predicted need for dosing at least every 6 h (Appendix C Table C1). Also similar to the every 8 h findings, several of the tested thresholds for age, CrCl, SCr, and DSI were statistically significant. Interestingly, TBSA, initiation within 4 days of injury, inhalation injury, male gender, or AKIN ≤ 1 were not found to significantly predict need for dosing at least every 6 h during univariable regression. Table 3 displays the highest performing multivariable models for the every 6 h analysis.

Based on the top performing models for each, 7 algorithms were built (Appendix D Table D1). Each algorithm produced a recommended initial regimen for each patient. Algorithms 1–4 recommended regimens utilizing dosing every 24, 12, or 8 h. Algorithms 5–7 were built by taking the highest performing model from 1 to 4, and adding recommendations for when to dose every 6 h in hopes of improving target attainment. Each algorithm was built to recommend loading doses of 25 mg/kg, dosing every 12 h for CrCl 79 −31 ml/min, and dosing every 24 h for CrCl ≤ 30 ml/min. Each dose was rounded to the nearest 250 mg increment with a maximum of 2500 mg. IBW was used to calculate CrCl and actual body weight used to calculate dose. Maintenance dose for models 1, 3, 4, and 5 utilized 18 mg/kg. Algorithms 2, 6, and 7 utilized 15 mg/kg for maintenance dose recommendations. The interval differences for each algorithm were significantly different (Appendix D Table D1). Each regimen was tested for accuracy of target attainment (Table 4). The highest performing algorithm was algorithm 6 with 26% resulting in a trough of 15–20 mg/L, 83% achieving an AUC ≥ 400 mghr/L, and 72% reaching an AUC 400 mghr/L without having a trough over 20 mg/L. Average predicted C_{max}, C_{min}, AUC was 34.5 mg/L, 13.7 mg/L, and 545 mghr/L, respectively. Fig. 1 demonstrates the odds of target attainment for each of the top 5 algorithms versus the current non-algorithm based practice (actual prescribed regimens herein).

Table 1 – Demographics for calculated vancomycin dosing interval required to attain a steady state trough of 15–20 mg/L.

Demographic	4 or 6 h (n = 36)	8 h (n = 54)	12 h (n = 30)
Age (years)[c]	35.6 ± 12.8	47.7 ± 16.1	60.1 ± 16.6
Age ≤ 50[a]	29 (81)	27 (50)	8 (27)
Age ≤ 40[a]	24 (67)	15 (28)	5 (17)
Age ≤ 30[a]	15 (42)	8 (15)	1 (3)
Age ≤ 25[a]	9 (25)	7 (13)	1 (3)
Age ≤ 20[a]	2 (6)	1 (2)	1 (3)
Male[a]	28 (78)	42 (78)	24 (80)
Weight (kg)[b]	83.6 (21.7, 175.5)	91 (50, 151.5)	81.7 (58.4, 140.9)
TBSA (%)[b]	13 (0.5, 55)	9.8 (0.1, 76)	12.5 (0.25, 79)
TBSA ≥ 10%[a]	23 (64)	27 (50)	17 (57)
DSI[b]	5 (2, 15)	6.5 (2, 30)	9 (2, 29)
AKIN ≥ 1[a,d]	10 (28)	11 (20)	22 (73)
CVVH[a]	1 (3)	2 (4)	6 (20)

Four patients received less frequent doses and were not included in this table (one received every 18 h and three every 24 h). AKIN, Acute Kidney Injury Network classification day of vancomycin initiation; CrCl, estimated creatinine clearance via Cockcroft-Gault; CVVH, continuous venovenous hemofiltration on day of sample collection; DSI, days since injury; TBSA, total body surface area burn.
[a] n (%).
[b] Median (range).
[c] Mean ± SD.
[d] AKIN 3 assigned to all patients started on CVVH, regardless of residual function or indication.

4. Discussion

This study utilized actual patient kinetics from a large cohort of thermally injured patients receiving vancomycin to build and find the best algorithm to guide empiric dosing. Unique to this study, the large sample included the entire spectrum of renal function and percent thermal injury. While only utilizing single center data, the top algorithm achieved the highest recorded success in the literature to date of therapeutic target attainment for intermittent infusion in patients with thermal injury.

This study did not exclude patients with renal dysfunction from analysis. Renal dysfunction is an exclusion in many studies, because it is known to impact clearance of many medications, such as vancomycin [10–13,25]. While some studies desire a pure clinical picture to eliminate potential confounders, the purpose of this study was to build and test an algorithm to generalize to all thermally injured patients. In truth, the pure patient is unrealistic when considering the

Table 2 – Highest performing logistic regression models for predicting recommended dosing at least every 8h.

Model		Odds ratio (95% confidence interval)	p	LRTS
1	CrCl ≥ 80	34.33 (9.54, 123.47)	<0.001	74.2
	AKIN ≥ 1	0.06 (0.02, 0.27)	<0.001	
	TBSA ≥ 10	4.43 (1.07, 18.34)	0.04	
2	CrCl ≥ 80	28.07 (8.5, 92.71)	<0.001	69.52
	AKIN ≥ 1	0.12 (0.04, 0.4)	<0.001	
3	CrCl ≥ 80	44.805 (13.22, 151.87)	<0.001	64.29
	DSI 2–4	6.2 (1.63, 23.54)	0.007	
4	CrCl ≥ 80	34.99 (11.25, 108.86)	<0.001	59.94
	DSI ≤ 11	3.94 (1.01, 15.36)	0.048	
5	CrCl ≥ 80	33.52 (11.34, 99.1)	<0.001	55.89

AKIN, Acute Kidney Injury Network classification day of vancomycin initiation; CrCl, estimated creatinine clearance (ml/min); DSI, days since injury; LRTS, Likelihood ratio test statistic; TBSA, percent total body surface area.

Table 3 – Highest performing logistic regression models for predicting recommended dosing at least every 6h.

Model		Odds ratio (95% confidence interval)	p	LRTS
1	CrCl ≥ 80	11.76 (1.36, 102.13)	0.025	45.62
	Age ≤ 40	4.54 (1.68, 12.24)	0.003	
	DSI ≤ 6	3.76 (1.41, 10.01)	0.008	
	SCr ≤ 0.8	2.74 (0.97, 7.77)	0.058	
2	CrCl ≥ 80	20.02 (2.47, 162.14)	0.005	41.83
	Age ≤ 40	3.89 (1.51, 10.01)	0.005	
	DSI ≤ 6	3.43 (1.33, 8.84)	0.011	
3	CrCl ≥ 80	10.17 (1.18, 85.15)	0.033	38.12
	Age ≤ 40	4.73 (1.84, 12.19)	0.001	
	SCr ≤ 0.8	2.39 (0.9, 6.4)	0.082	
4	CrCl ≥ 80	18.7 (2.33, 149.88)	0.006	37.92
	Age ≤ 40	4.31 (1.71, 10.87)	0.002	
	TBSA ≥ 10	2.23 (0.88, 5.64)	0.091	
5	CrCl ≥ 80	16.14 (2.05, 127.28)	0.008	34.97
	Age ≤ 40	4.15 (1.67, 10.27)	0.002	

CrCl, estimated creatinine clearance (ml/min); DSI, days since injury; LRTS, Likelihood ratio test statistic; SCr, serum creatinine (mg/dL); TBSA, percent total body surface area.

Table 4 – Algorithm performance based on trough and area under the curve (AUC).

Algorithm	Trough <10[a,b]	Trough 10–20[a,b]	Trough 15–20[a,b]	Trough >20[a,b]	AUC >400[a,b]	AUC >400 without overdose[a,b,c]
1	28 (23)	72 (58)	35 (28)	24 (19)	110 (89)	86 (69)
2	38 (31)	73 (61)	28 (23)	10 (8)	97 (78)	87 (70)
3	50 (40)	66 (58)	26 (21)	8 (7)	86 (69)	78 (63)
4	71 (57)	47 (38)	15 (12)	6 (5)	64 (52)	58 (47)
5	17 (14)	77 (62)	39 (32)	30 (24)	116 (94)	86 (69)
6	29 (23)	81 (65)	32 (26)	14 (11)	103 (83)	89 (72)
7	34 (27)	77 (62)	28 (23)	13 (11)	100 (81)	87 (70)

[a] Results presented as n (%).
[b] Troughs measured in mg/L and AUC mghr/L.
[c] Overdose defined as trough >20 mg/L.

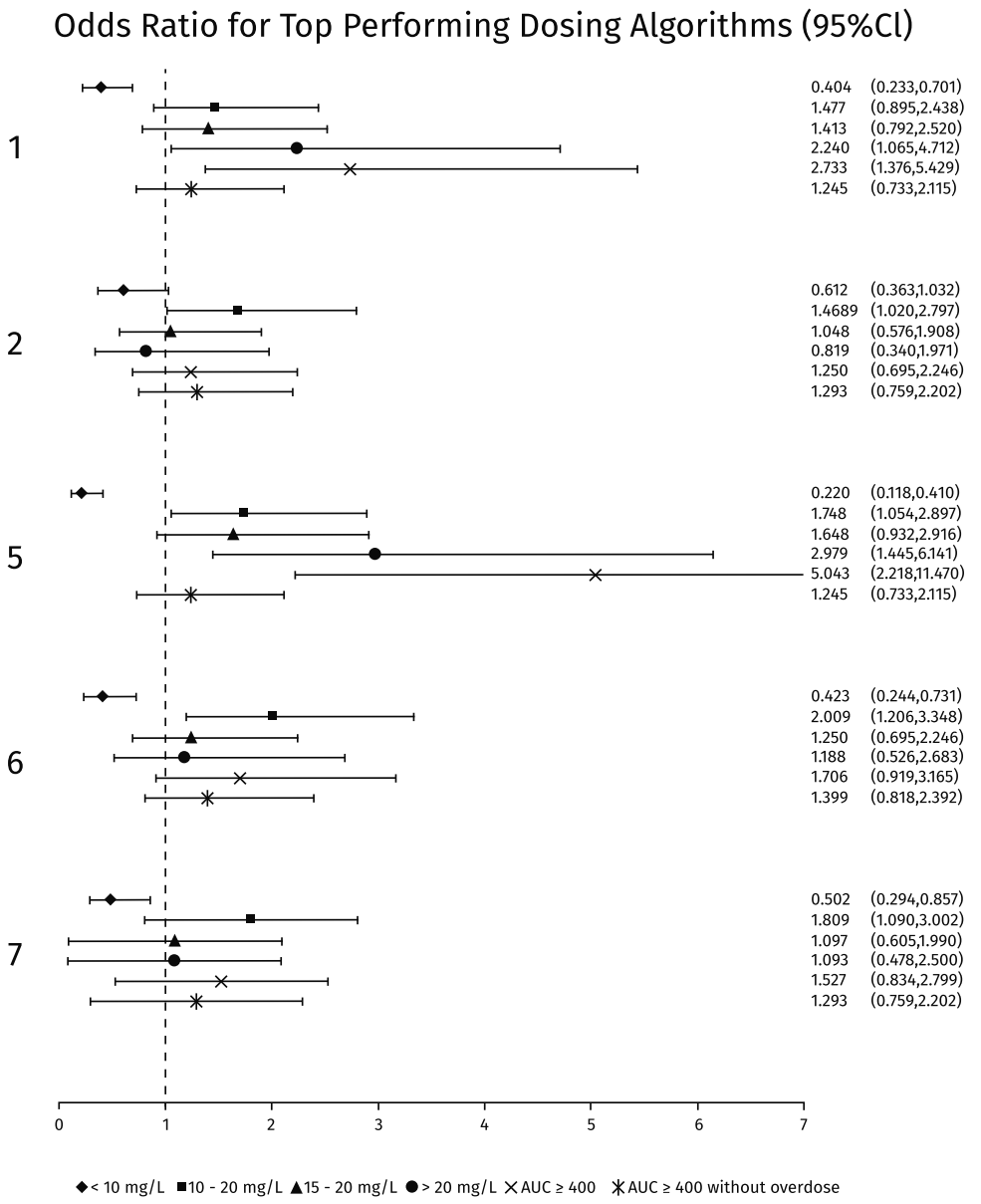

Fig. 1 – Odds Ratio and 95% confidence intervals of the top performing algorithms for most accurately prescribing empiric vancomycin doses in thermally injured patients. Performance was measured versus actual prescribed regimen received by each patient and presented as odds of attaining trough values in each range and AUC (mghr/L).

thermally injured critical care population, as renal dysfunction is only one of many clinical battles that must be regarded. Including such a range of patients increases the external validity of this study and dosing algorithm. For completeness, algorithm 6 performed even better in the subcohort of patients with no renal insufficiency at time of vancomycin initiation (27% resulted with a trough <10mg/L, 28% 15–20mg/L, 7%> 20mg/L, and 82% achieved an AUC≥400mghr/L without overdosing).

As mentioned, selection bias for determining which variables could be significant was possible. For example, AKIN score was significant for determining dosing frequency and AKIN≥1 was chosen for analysis based on successful anecdotal practice to be preemptive and cease progression of renal dysfunction earlier. In fact, 31 patients had an AKIN classification of 1 at the start of vancomycin and 77% had resolution with 48h. Also, only 4 patients had an AKIN classification of 2 the day of initiation (2 recovered within 48h). If similar aggressive tactics are not followed to cease renal dysfunction progression, AKIN 1 and likely 2 may be of more importance externally.

Although estimated CrCl may not fully depict filtration abilities of the kidneys, this study agrees with previous literature in thermally injured patients on the utility of the Cockcroft-Gault equation to guide and adjust vancomycin dosing [10,11,13,27]. While useful, CrCl only partially explained vancomycin clearance in this cohort ($y=0.638x+61.204$; $r^2=0.333$). For interest, application of population kinetics from

the variables in this study would be difficult. The best regression model for predicting $k_e = 0.293 - (0.000169 \times \text{Age}) - (0.0783 \times \text{SCr at initiation})$ ($r^2 = 0.335$). The authors concur with previous hypotheses that the extra-renal elimination of vancomycin can be due in part to burn wound loss, especially since many of the cohort were within the first two weeks of admission, with large affected areas, and prior to complete wound excision and/or grafting [11,14]. Since early wound closure reduces metabolic demand and also protein loss, it will be interesting for future studies to also analyze impact of early wound closure and extra-renal loss of some medications [10,28].

The best model utilized only 1 variable to determine 8 hourly dosing, but 3 for dosing 6 hourly to increase selectivity for such frequent administration. Models 2, 4, and 5 (Table 3) for predicting dosing every 6 h were not considered for algorithms, based on the potential for inclusion of a 40 year old patient with a SCr of 1.3 to still have CrCl ≥ 80 and the algorithm recommending vancomycin be dosed every 6 h. While differences in muscle mass can falsify the Cockcroft-Gault equation's utility and some patients with such clearance may benefit from such frequent administration, it is uncommon and empiric recommendations for dosing every 6 h or more in this patient should warrant apprehension. Only 5 patients in the present cohort were under a body mass index (BMI) of 20 kg/m^2. All 5 patients with dosing at least every 6 h, with 2 every 4 h. Previously, the authors found TBSA to predict clearance and total daily dose in a multivariable model of a cohort of these patients without renal dysfunction as a confounder [14]. TBSA had less impact in the overall cohort, because of the increased incidence of renal failure in the patients with higher TBSA. DSI performed very well during modeling with ≤6 and ≤11 being standouts for dosing every 6 h with statistically significant odds ratios (2.6 and 5, respectively). DSI ≤ 6 outperformed ≤11 and was included in algorithm 7. Including DSI demonstrated acceptable performance, but was not the best performer due to allocation of to many patients beyond DSI 6 to an every 8 h regimen that would have benefited from more frequent dosing.

There are mixed data on which target and risk factors produce the highest risk of nephrotoxicity. There are single center studies supporting and refuting greatest risk with troughs exceeding 15 mg/L [16,17,29]. Some suggest the greatest risk is associated with troughs exceeding 20 mg/L and in presence of additional risk factors [30,31]. Others suggest total daily dose, AUC >600 mg hr/L, AUC >700 mg hr/L, or AUC >1300 mg hr/L to be most predictive [30,32–34]. The present algorithm may seem aggressive to some practitioners; however, only 14 patients (11%) had predicted trough >20 mg/L. Only 3 patients had troughs >25 mg/L. Four of the 14 were dosed every 6 h and overdose was not severe (trough range of 22–26 mg/L). Three underwent dosing every 18 or 24 h dosing when every 12 h was recommended by the algorithm. Half had excessively small Vd (<0.5 L/kg) and 64% had an AKIN ≥ 1 at vancomycin initiation, which emphasizes the importance of focus on fluid status during vancomycin initiation. Thirty-five and 14% were predicted to exceed an AUC of 600 and 700 mg hr/L, respectively, with half having an AKIN ≥ 1 at vancomycin initiation. Despite aggressive targeting of 15–20 mg/L during Phase 1, only 13 (17%) of the 77 patients that did not have renal dysfunction prior to vancomycin initiation progressed to AKIN ≥ 1 at any point during vancomycin therapy and only 9% to AKIN ≥ 2, which is greater than a 50% reduction from recent published literature on incidence of possible vancomycin-induced nephrotoxicity. As with the majority of pharmacokinetic studies in thermally injured patients, the authors agree that extreme variability exists and frequent monitoring of trough concentrations should occur to adjust regimens for likely accumulation, if course is prolonged. An important point to emphasize is the frequency in which the authors' monitor concentrations. The authors' recommend two concentrations (C_1, 1 h after infusion ends for third maintenance dose and C_2, as near and prior to beginning of the fourth maintenance dose) to be drawn during the initial regimen to establish ke, half-life, Vd, clearance, trough, and AUC. In absence of significant suspected changes in volume or clearance, troughs can be monitored once weekly with daily monitoring of renal function.

This study did not consider infection source, indication, pathogen, or outcomes. The target of 15–20 mg/L versus AUC ≥ 400 mg hr/L continues to be debated [15,23–25]. For the audience, both targets were analyzed and presented within this study. Additionally, a post-hoc analysis was performed for those desiring a target of 10–20 mg/L, similar to that done for a target of 15–20 mg/L. The best algorithm targeting 10-20 mg/L only differed by substituting CrCl of 170 ml/min instead of 80 ml/min for dosing every 6 h. Similar performance is not surprising based on the average trough of 13.7 mg/L produced by algorithm 6 (29% resulted with a trough <10 mg/L, 62% 10–20 mg/L, 9% >20 mg/L, and 71% achieved an AUC ≥ 400 mg hr/L without overdosing). An AUC ≥ 400 mg hr/L was selected based on the guidance to achieve an AUC_{24}:MIC >400 [24,35,36]. While MIC was not individually analyzed in the present study, a recent study from the authors' institution reviewed institution data of MIC values for all *Staphylococcus* isolates reported since 2003 [37]. Not only did MICs not increase over the study period, by 2008 values exceeding 1 mcg/mL were nearly non-existent. Vitek® 2 issues notwithstanding, a target AUC of 400 mg hr/L should be adequate at the present institution. This algorithm, and perhaps vancomycin, may not be appropriate for institutions with frequent MICs exceeding 1 mcg/mL.

As with any retrospective study, the present study has limitations. Data utilized was collected retrospectively and subject to record bias. Pharmacokinetic data was part of a cohort of patients used to establish factors that would contribute to augmented clearance and total daily dose. Calculation errors were possible but likely minimized, as they were independently performed and cross-checked by two clinicians. Algorithm validation was projected and not validated prospectively, but will be subject of future validation studies. External validity is stronger than existing literature, but still not without potential error. The recommended dose of 15 mg/kg presented within this study will exhibit inter and intra-patient variability and follow closely with patient fluid status secondary to the hydrophilic nature of vancomycin. Our median Vd was 0.63 L/kg and may differ

at other institutions. It may be difficult to extrapolate findings to all sites utilizing continuous venovenous hemofiltration (CVVH), as specific CVVH data was not collected beyond dichotomous values. While 20 patients received CVVH at some point of the stay, only 10 patients were on CVVH prior to initial sampling. Data of the study sites CVVH practice has been published previously and will aid other sites application of results [38]. Although this study analyzed 41 variables for significance of predicting dosing every 6 and 8 h, it was a single center study, and other centers may identify additional variables significant in their patients. As eluded earlier, dosing every 12, 18 and 24 h were underrepresented in this cohort and represents a need of focus for future algorithms. Similarly, the algorithm could have performed better, as 6 patients were underdosed and actually underwent dosing every 4 h due to excessive clearance. Caution is emphasized for patients with baseline renal dysfunction, risk factors for nephrotoxicity, or receiving renal replacement therapy, as such patients benefit from extra vigilance.

5. Conclusion

The present study demonstrates potential to improve empiric dosing regimens for intermittent infusion vancomycin in the largest thermally injured pharmacokinetic cohort to date. Utilizing a dose of 15 mg/kg, CrCl ≥ 80 ml/min as the threshold for dosing every 8 h, and age ≤ 40 years old and SCr ≤ 0.8 mg/dL as additional qualifications for dosing every 6 h improves odds of initial target attainment in thermally injured patients. Reducing delay in ideal concentration achievement could lead to improved microbiologic and clinical outcomes and should be subject of future research.

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Conflict of interest statement

We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.

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Appendix A.

Table A1 – Variables analyzed for predicting dosing at least every 6 and 8 h.

Age (years)[b]	DSI[b]	SCr at initiation[b]	CrCl[b]
Age ≤ 20 (years)[a]	DSI 2–4[a]	SCr ≤ 1[a]	CrCl ≥ 180[a]
Age ≤ 25(years)[a]	DSI ≤ 5[a]	SCr ≤ 0.9[a]	CrCl ≥ 170[a]
Age ≤ 30 (years)[a]	DSI ≤ 6[a]	SCr ≤ 0.8[a]	CrCl ≥ 120[a]
Age ≤ 40 (years)[a]	DSI ≤ 7[a]	SCr ≤ 0.7[a]	CrCl ≥ 110[a]
Age ≤ 50 (years)[a]	DSI ≤ 8[a]	SCr ≤ 0.6[a]	CrCl ≥ 100[a]
Sex[a]	DSI ≤ 9[a]	AKIN	CrCl ≥ 90[a]
TBSA[b]	DSI ≤ 10[a]	AKIN ≥ 1[a]	CrCl ≥ 80[a]
TBSA ≥ 10[a]	DSI ≤ 11[a]		CrCl ≥ 70[a]
Inhalation Injury[a]	DSI ≤ 12[a]		CrCl ≥ 60[a]
	DSI ≤ 13[a]		CrCl ≥ 50[a]
	DSI ≤ 14[a]		

AKIN, Acute Kidney Injury Network classification day of vancomycin initiation; CrCl, estimated creatinine clearance (ml/min); DSI, days since injury; SCr, serum creatinine (mg/dL) day of vancomycin initiation; TBSA, total body surface area burn (percent).
[a] Dichotomous variable.
[b] Continuous variable.

Appendix B.

Table B1 – Significant variables for predicting dosing at least every 8 h.

	Odds ratio (95% confidence interval)	p
Age (years)	0.94 (0.91, 0.96)	<0.001
Age ≤ 50 (years)[a]	5.04 (2.10, 12.09)	<0.001
Age ≤ 40 (years)[a]	3.91 (1.47, 10.35)	0.006
Age ≤ 30 (years)[a]	12 (1.56, 92.62)	0.017
DSI[b]	0.93 (0.87, 0.99)	0.024
DSI ≤ 12[a]	3.33 (1.24, 8.95)	0.017
DSI ≤ 11[a]	3.44 (1.32, 8.94)	0.011
DSI ≤ 10[a]	3.11 (1.21, 7.97)	0.018
DSI ≤ 7[a]	2.35 (1.05, 5.26)	0.037
DSI 2 – 4[a]	3.41 (1.29, 9.05)	0.014
SCr[b]	0.01 (0.002, 0.08)	<0.001
SCr ≤ 1.0[a]	8.77 (3.58, 21.49)	<0.001
SCr ≤ 0.9[a]	5.75 (2.44, 13.55)	<0.001
SCr ≤ 0.8[a]	6.39 (2.41, 16.95)	<0.001
SCr ≤ 0.7[a]	6.28 (2.04, 19.29)	0.001
SCr ≤ 0.6[a]	8.83 (1.13, 68.79)	0.038
CrCl[b]	1.06 (1.04, 1.09)	<0.001
CrCl ≥ 120[a]	12.24 (2.76, 54.19)	<0.001
CrCl ≥ 110[a]	18.29 (4.13, 80.92)	<0.001
CrCl ≥ 100[a]	32 (7.18, 142.60)	<0.001
CrCl ≥ 90[a]	21.85 (6.95, 68.71)	<0.001
CrCl ≥ 80[a]	33.52 (11.34, 99.10)	<0.001
CrCl ≥ 70[a]	24.60 (8.74, 69.25)	<0.001
CrCl ≥ 60[a]	17.73 (6.09, 51.68)	<0.001
CrCl ≥ 50[a]	18.33 (3.76, 89.35)	<0.001

Table B1 (continued)

	Odds ratio (95% confidence interval)	p
AKIN	0.23 (0.13, 0.41)	<0.001
AKIN ≥ 1[a]	0.09 (0.04, 0.24)	<0.001

AKIN, Acute Kidney Injury Network classification day of vancomycin initiation; CrCl, estimated creatinine clearance (ml/min); DSI, days since injury; SCr, serum creatinine (mg/dL).
[a] Dichotomous variable.
[b] Continuous variable.

Appendix C.

Table C1 – Significant variables for predicting recommended dosing at least every 6h.

	Odds ratio (95% confidence interval)	p
Age	0.94 (0.91, 0.96)	<0.001
Age ≤ 50[a]	5.45 (2.16, 13.77)	<0.001
Age ≤ 40[a]	6.82 (2.89, 16.08)	<0.001
Age ≤ 30[a]	5.57 (2.19, 14.18)	<0.001
Age ≤ 25[a]	3.33 (1.17, 9.50)	0.024
DSI	0.90 (0.82, 0.99)	0.026
DSI ≤ 11[a]	5.00 (1.1, 22.65)	0.037
DSI ≤ 7[a]	2.60 (1.12, 6.03)	0.026
DSI ≤ 6[a]	2.61 (1.14, 5.94)	0.023
SCr	0.03 (0.005, 0.23)	<0.001
SCr ≤ 1.0[a]	6.29 (1.78, 22.14)	0.004
SCr ≤ 0.9[a]	4.36 (1.65, 11.52)	0.003
SCr ≤ 0.8[a]	3.79 (1.65, 8.69)	0.002
SCr ≤ 0.7[a]	2.67 (1.20, 5.92)	0.016
SCr ≤ 0.6[a]	3.86 (1.44, 10.39)	0.007
CrCl	1.03 (1.01, 1.04)	<0.001
CrCl ≥ 170[a]	7.00 (2.00, 24.56)	0.002
CrCl ≥ 120[a]	3.35 (1.49, 7.56)	0.004
CrCl ≥ 110[a]	4.00 (1.77, 9.05)	<0.001
CrCl ≥ 100[a]	8.75 (3.29, 23.27)	<0.001
CrCl ≥ 90[a]	10.05 (3.28, 30.85)	<0.001
CrCl ≥ 80[a]	26.6 (3.49, 202.95)	0.002
AKIN	0.49 (0.27, 0.9)	0.02

AKIN, Acute Kidney Injury Network classification day of vancomycin initiation; CrCl, estimated creatinine clearance (ml/min); DSI, days since injury; SCr, serum creatinine (mg/dL).
[a] Dichotomous variable.

Appendix D.

Table D1 – Vancomycin algorithms tested.

Algorithm[a]	Maintenance dose	Interval[a]	Requirements
1	18mg/kg	Every 8h	CrCl ≥ 80
2	15mg/kg	Every 8h	CrCl ≥ 80
3	18mg/kg	Every 8h	CrCl ≥ 80 AKIN ≤ 1

(continued on next page)

Table D1 (continued)

Algorithm[a]	Maintenance dose	Interval[a]	Requirements
4	18mg/kg	Every 8h	CrCl ≥ 80 AKIN ≤ 1 TBSA ≥ 10
5	18mg/kg	Every 6h[b]	CrCl ≥ 80 Age ≤ 30[c] SCr ≤ 0.6
		Every 8h	CrCl ≥ 80
6	15mg/kg	Every 6h[b]	CrCl ≥ 80 Age ≤ 30[c] SCr ≤ 0.6
		Every 8h	CrCl ≥ 80
7	15mg/kg	Every 6h[b]	CrCl ≥ 80 Age ≤ 30[c] SCr ≤ 0.6 DSI ≤ 6
		Every 8h	CrCl ≥ 80

AKIN, Acute Kidney Injury Network classification day of vancomycin initiation; CrCl, estimated creatinine clearance (ml/min); DSI, days since injury; SCr, serum creatinine (mg/dL); TBSA, total body surface area burned (percent).
[a] Each algorithm was built to recommend loading doses of 25mg/kg, dosing every 12h for CrCl 79–31ml/min, and dosing every 24h for CrCl ≤ 30ml/min.
[b] All requirements must be met to be dosed every 6h.
[c] Years old.

REFERENCES

[1] Bonate PL. Pathophysiology and pharmacokinetics following burn injury. Clin Pharmacokinet 1990;18:118–30.
[2] Hill DM, Sinclair SE, Hickerson WL. Rational selection and use of antimicrobials in patients with burn injuries. Clin Plast Surg 2017;44:521–34.
[3] Zaske E, Cipolle RJ, Solem LD, Strate RJ. Rapid individualization of gentamicin dosage regimens in 66 burn patients. Burns 1981;7(3):215–20.
[4] Boucher BA, Hickerson WL, Kuhl DA, Bombassaro AM, Jaresko GS. Imipenem pharmacokinetics in patients with burns. Clin Pharmacol Ther 1990;48(August (2)):130–7.
[5] Boucher BA, King SR, Wandschneider HL, Hickerson WL, Hanes SD, Herring VL, et al. Fluconazole pharmacokinetics in burn patients. Antimicrob Agents Chemother 1998;42(April (4)):930–3.
[6] Lesne-Hulin A, Bourget P, Ravat F, Goudin C, Latarjet J. Clinical pharmacokinetics of ciprofloxacin in patients with major burns. Eur J Clin Pharmacol 1999;55(September (7)):515–9.
[7] Conil JM, Georges B, Breden A, Segonds C, Lavit M, Seguin T, et al. Increased amikacin dosage requirements in burn patients receiving a once-daily regimen. Int J Antimicrob Agents 2006;28(September (3)):226–30.
[8] Lovering AM, Le Floch R, Hovsepian L, Stephanazzi J, Bret P, Birraux G, et al. Pharmacokinetic evaluation of linezolid in patients with major thermal injuries. J Antimicrob Chemother 2009;63(March (3)):553–9.
[9] Brater DC, Bawdon RE, Anderson SA, Purdue GF, Hunt JL. Vancomycin elimination in patients with burn injury. Clin Pharmacol Ther 1986;39:631–4.

[10] Garrelts JC, Peterie JD. Altered vancomycin dose vs. serum concentration relationship in burn patients. Clin Pharmacol Ther 1988;44:9–13.
[11] Dolton M, Xu H, Cheong E, Maitz P, Kennedy P, Gottlieb T, et al. Vancomycin pharmacokinetics in patients with severe burn injuries. Burns 2010;36:469–76.
[12] Rybak MJ, Albrecht LM, Berman JR, Warbasse LH, Svensson CK. Vancomycin pharmacokinetics in burn patients and intravenous drug abusers. Antimicrob Agents Chemother 1990;34:792–5.
[13] Elligsen M, Walker SA, Walker SE, Simor A. Optimizing initial vancomycin dosing in burn patients. Burns 2011;37:406–14.
[14] Elder K, Hill DM, Hickerson WL. Characterization of variables for potential impact on vancomycin pharmacokinetics in thermal or inhalation injury. Burns 2017;(October):S0305–4719.
[15] Rybak M, Lomaestro B, Rotschafer JC, Moellering Jr R, Craig W, Billeter M, et al. Therapeutic monitoring of vancomycin in adult patients: a consensus review of American Society of Health-System Phramacists, the Infectious Diseases Society of America, and the Society of Infectious Diseases Pharmacists. Am J Health Syst Pharm 2009;66:82–98.
[16] 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;57:732–44.
[17] Neely MN, Kato L, Youn G, Kraler L, Bayard D, van Guilder M, et al. Prospective trial on the use of trough concentration versus area under the curve to determine therapeutic vancomycin dosing. Antimicrob Agents Chemother 201862 (Januray (2)) e02042-17.
[18] Hogan BK, Wolf SE, Hospenthal DR, D'Avignon LC, Chung KK, Yun HC, et al. Correlation of American Burn Association sepsis criteria with the presence of bacteremia in burned patients admitted to the intensive care unit. J Burn Care Res 2012;33(3):371–8.
[19] Mann-Salinas EA, Baun MM, Meininger JC, Murray CK, Aden JK, Wolf SE, et al. Novel predictors of sepsis outperform the American Burn Association sepsis criteria in the burn intensive care unit patient. J Burn Care Res 2013;31(1):31–43.
[20] Hill DM, Percy MD, Velamuri SR, Lanfranco J, Romero Legro, Sinclair SE, et al. Predictors for identifying burn sepsis and performance versus existing criteria. J Burn Care Res 2018 (May), doi:http://dx.doi.org/10.1093/jbcr/iry022.
[21] Greenhalgh DG, Saffle R, Holmes 4th JH, Gamelli RL, Palmieri TL, Horton JW, et al. American Burn Association consensus conference to define sepsis and infection in burns. J Burn Care Res 2007;28:776–90.
[22] Ackerman BH, Guilday RE, Reigart CL, Patton ML, Haith LR. Evaluation of the relationship between elevated vancomycin trough concentrations and increased efficacy and/or toxicity. J Burn Care Res 2013;34:e1–9.
[23] Moise-Broder A, Forrest A, Birmingham MC, Schentag JJ. Pharmacodynamics of vancomycin and other antimicrobials in patients with *Staphylococus aureus* lower respiratory tract infections. Clin Pharmacokinet 2004;43:925–42.
[24] Holmes NE, Turnidge JD, Munckhof WJ, Robinson JO, Korman TM, O'Sullivan MV, et al. Vancomycin AUC/MIC ratio and 30-day mortality in patients with *Staphylococcus aureus* bacteremia. Antimicrob Agents Chemother 2013;57(April (4)):1654–63.
[25] Akers KS, Cota JM, Chung KK, Renz EM, Mende K, Murray CK. Serum vancomycin levels resulting from continuous or intermittent infusion in critically ill burn patients with or without continuous renal replacement therapy. J Burn Care Res 2012;33:e254–62.
[26] Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976;16:31–41.
[27] Conil JM, Georges B, Breden A, Ruiz S, Cougot P, Fourcade O, et al. Estimation of glomerular filtration rate to adjust vancomycin dosage in critically ill patients: superiority of the Chronic Kidney Disease Epidemiology Collaboration equation? Anaesth Intensive Care 2014;42(March (2)):178–84.
[28] Dickerson RN, Gervasio JM, Riley ML, Murrell JE, Hickerson WL, Kudsk KA, et al. Accuracy of predictive methods to estimate resting energy expenditure of thermally-injured patients. JPEN J Parenter Enteral Nutr 2002;26(January–February (1)):17–29.
[29] Chuma M, Makishima M, Imai R, Tochikura N, Suzuki S, Kuwana T, et al. Relationship between initial vancomycin trough levels and early-onset vancomycin-associated nephrotoxicity in critically ill patients. Ther Drug Monit 2018;40(February (1)):109–14.
[30] Lodise TP, Patel N, Lomaestro BM, Rodvold KA, Drusano GL. Relationship between initial vancomycin concentration-time profile and nephrotoxicity among hospitalized patients. Clin Infect Dis 2009;49(August (4)):507–14.
[31] Wong-Beringer A, Joo J, Tse E, Beringer P. Vancomycin-associated nephrotoxicity: a critical appraisal of risk with high-dose therapy. Int J Antimicrob Agents 2011;37(February (2)):95–101.
[32] Lodise TP, Lomaestro B, Graves J, Drusano GL. Larger vancomycin doses (at least four grams per day) are associated with an increased incidence of nephrotoxicity. Antimicrob Agents Chemother 2008;52(April (4)):1330–6.
[33] Suzuki Y, Kawasaki K, Sato Y, Tokimatsu I, Itoh H, Hiramatsu K, et al. Is peak concentration needed in therapeutic drug monitoring of vancomycin? A pharmacokinetic-pharmacodynamic analysis of patients with methicillin-resistant *Staphylococcus aureus* pneumonia. Chemotherapy 2012;58(4):308–12.
[34] Zasowski EJ, Murray KP, Trinh TD, Finch NA, Pogue JM, Mynatt RP, et al. Identification of vancomycin exposure-toxicity thresholds in hospitalized patients receiving intravenous vancomycin. Antimicrob Agents Chemother 201862(January (1)) e01684-17.
[35] Tenover FC, Moellering RC. The rationale for revising the clinical and laboratory standards institute vancomycin minimal inhibitory concentration interpretive criteria for *Staphylococcus aureus*. Clin Infect Dis 2007;44(May (9)):1208–15.
[36] Hsu DI, Hidayat LK, Quist R, Hindler J, Karlsson A, Yusof A, et al. Comparison of method-specific vancomycin minimum inhibitory concentration values and their predictability for treatment outcome of meticillin-resistant *Staphylococcus aureus* (MRSA) infections. Int J Antimicrob Agents 2008;32 (November (5)):378–85.
[37] Smith K, Clement P. Evaluating the trend of vancomycin minimum inhibitory concentration (MICs) in trauma intensive care unit patients with *Staphylococcus aureus* bacteremia or pneumonia. American Society of Health-System Pharmacists 46th annual midyear meeting. December 4. New Orleans, LA.
[38] Boucher BA, Hudson JQ, Hill DM, Swanson JM, Wood G, Laizure SC, et al. Pharmacokinetics of imipenem/cilastatin burn intensive care unit patients undergoing high-dose continuous venovenous hemofiltration. Pharmacotherapy 2016;36 (December (12)):1229–37.