Refining and Validating a High-Target Vancomycin Nomogram in Young and Elderly Patients

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Background

- High vancomycin trough levels (15-20 mg/L) and AUC_{24}/MIC ratios of ≥ 400 are recommended to improve clinical success for invasive infections and methicillin-resistant *S. aureus*[1]
- In 2009, a high target vancomycin dosing nomogram was developed at Vancouver General Hospital (VGH) and St. Paul's Hospital (SPH) with limited number of subjects in the < 40 and ≥ 70 year old age groups during nomogram development
- Concern for the reliability of the nomogram in young and elderly populations due to altered pharmacokinetics

Objectives

Primary

- Characterize vancomycin pharmacokinetic (PK) parameters
- Refine and validate high-target vancomycin nomogram in age categories of 20-39 and 70-89 years old

Secondary

- Characterize peak vancomycin levels
- Calculate AUC_{24}/MIC ratios
  - Based on differences in AUC_{24} between patient specific PK parameters and population estimates

Methods

Design: Retrospective healthcare record review conducted at VGH and SPH in Vancouver, BC

Patients:

- Hospitalized patients who required intravenous vancomycin
- Ages 19-39 or ≥ 70 years old
- Documented serum creatinine (SCr) and weight
- Stable renal function
  - No change in SCr by ≥ 1.5 times from baseline or ≥ 26.5 umol/L in 48 hours[2]
- *Refining Group*: pair of pre- and post-infusion levels around 3rd dose or later
- *Validation Group:* steady-state vancomycin trough level between 15-20 mg/L

Exclusion criteria:

- Renal failure, on hemodialysis, or SCr > 180 umol/L
- Levels drawn inappropriately
- Dosing information or sampling times missing or unclear

Data Analysis:

- *Refining Group:* use average of patient specific PK parameters to estimate appropriate dosing interval to construct refined nomogram
- *Validation Group:* compare actual dosing interval and predicted dosing intervals using refined nomogram
- AUC_{24}/MIC ratios using hypothetical MICs of 0.5 mg/L, 1.0 mg/L, 1.5 mg/L, and 2.0mg/L
  - Vancomycin clearance calculation using Sawchuk-Zaske method[3] (patient specific) and Rodvold equation[4] (population estimate) for AUC_{24} calculation

Table 1: Baseline Characteristics

Characteristic	Refining Group (n=31)	Validation Group (n=31)
Age, years ± SD •Young (19-39) •Elderly (≥70)	 30.6 ± 3.8 81.2 ± 7.3	 27.7 ± 6.2 79.3 ± 4.3
Male (%)	19 (61.3)	53 (66.3)
Indication for IV vancomycin (%) •Empiric *S. aureus* coverage •MRSA infection •Coagulase negative *Staphylococcus* •Other	 17 (54.8) 6 (19.4) 4 (12.9) 4 (12.9)	 17 (54.8) 10 (32.3) 3 (9.7) 1 (3.2)

Table 2: PK Parameters for Refining Group

Volume of Distribution (L/kg)				
SCr (umol/L)	20-29 years (n=5)	30-39 years (n=5)	70-79 years (n=9)	≥ 80 years (n=12)
≤ 60	0.7	0.6	1.3	0.9
61-80	0.8	0.8	0.7	1.2
81-100		0.7	1.2	0.9
121-140		0.5		0.9
Elimination Rate Constant, K (h^{-1})				
SCr (umol/L)	20-29 years (n=5)	30-39 years (n=5)	70-79 years (n=9)	≥ 80 years (n=12)
≤ 60	0.1639	0.1938	0.0649	0.0568
61-80	0.1084	0.1138	0.0678	0.0375
81-100		0.0899	0.0558	0.0451
121-140		0.0570		0.0648
Half-life (h)				
SCr (umol/L)	20-29 years (n=5)	30-39 years (n=5)	70-79 years (n=9)	≥ 80 years (n=12)
≤ 60	4.3	3.6	10.7	13.7
61-80	6.4	6.2	13.1	19.7
81-100		7.7	13.5	15.4
121-140		12.2		10.7

Figure1: Average Vancomycin Dose (mg/kg)

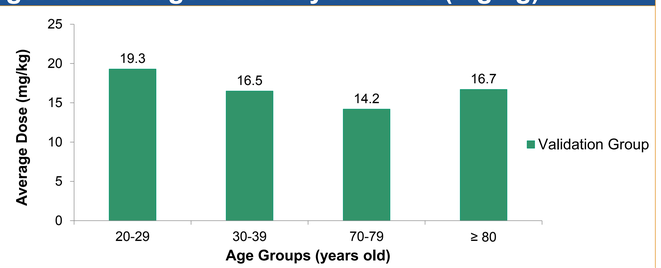

Table 3: Extrapolated Peak Concentration

	Trough 15-20 mg/L (n=8)	Trough >20 mg/L (n=6)	Trough < 15 mg/L (n=17)
Average, mg/L ± SD	40.5 ± 6.9	39.6 ± 3.8	26.7 ± 6.8
Min, mg/L	29.8	32.1	15.0
Max, mg/L	53.2	43.5	41.5

Refined Nomogram

SCr (umol/L)	Age						
	20-29	30-39	40-49	50-59	60-69	70-79	80-89
≤ 60	6	6-8	8	8	8-12	12	12
61-80	8	8	8-12	12	12	12	12-18
81-100	12	12	12	12	12-18	18	18
101-120	12	12	12-18	18	18	18	18
121-140	12	18	18	18	18	18-24	
141-160	18	18	18	18-24	24		
161-180	18-24	24	24	24			

Predictive success in young and elderly population = 58.1%

Table 4: AUC_{24}/MIC Ratios

Overall (n=31)	MIC = 0.5 mg/L	MIC = 1.0 mg/L	MIC = 1.5 mg/L	MIC = 2.0 mg/L
Sawchuk-Zaske (patient individualized)	1081.64 ± 305.41	540.82 ± 152.70	360.55 ± 101.80	270.41 ± 76.35
Rodvold (population estimate)	858.54 ± 207.49	429.27 ± 103.74	286.18 ± 69.16	214.64 ± 51.87

* Data presented as average ± SD
Wilcoxon Signed Rank Test: Z = -3.802, p = 0.0001

Trough 15-20 mg/L (n=8)	MIC = 0.5 mg/L	MIC = 1.0 mg/L	MIC = 1.5 mg/L	MIC = 2.0 mg/L
Sawchuk-Zaske (patient individualized)	1310.95 ± 116.90	655.48 ± 58.45	435.98 ± 38.97	327.74 ± 29.23
Rodvold (population estimate)	903.93 ± 174.15	451.96 ± 87.08	301.31 ± 58.05	225.98 ± 43.54

* Data presented as average ± SD
Wilcoxon Signed Rank Test: Z = -2.521, p = 0.012

Conclusion

- Wide inter-patient variability in PK parameters of patients 20-39 and ≥ 70 years of age
- Nomogram serves as an initial tool for empiric dosing of high-target vancomycin
- Available PK parameters and frequent use of higher doses (>15 mg/kg) to achieve target drug levels in young patients with good renal function suggest the need for Q6H dosing of vancomycin
- Peak vancomycin concentrations extrapolated to end of infusion were not excessively high when troughs of 15-20 mg/L were achieved
- AUC_{24} of vancomycin is higher as calculated by the Sawchuk-Zaske method versus the Rodvold equation, resulting in statistically different AUC_{24}/MIC ratios
- AUC_{24}/MIC ratios of ≥ 400 were achievable with vancomycin troughs of 15-20 mg/L at MICs ≤ 1.5 mg/L in our patient population
- Limitations:
  - Small sample size
  - Retrospective observational approach to nomogram refinement and validation

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