Poster
#1574

Predictive ability and bias of vancomycin population PK models in an obese adult population

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Background

- Accurate dosing of vancomycin is difficult due to high inter-individual variability of vancomycin pharmacokinetics (PK) and is particularly challenging in the obese population
- Vancomycin is hydrophilic, yet total body weight (TBW) has traditionally been used for dosing in both general and obese populations
- A wide number of vancomycin PK models have been published, including a 1-compartment model by Buelga DS et al. *(Antimicrob. Agents Chemother.* 2005:4934-4941), a 2-compartment model by *Goti V* et al. *(Ther. Drug Monitor* 2018;40:212-221), and a 1-compartment model designed specifically for use in the obese with TBW as body size metric as described by Adane et al. *(Pharmacother.* 2015;35:127-39)
- The Adane model for use in obese patients was developed using a relatively small cohort (*N* = 31) with a body mass index (BMI) ≥ 40 kg/m2

Objectives

- Evaluate the performance of published vancomycin PK models in a large dataset of routine clinical data obtained from an obese population with sizes reflecting the current obese patient population
- Develop a novel vancomycin PK model for Bayesian dosing

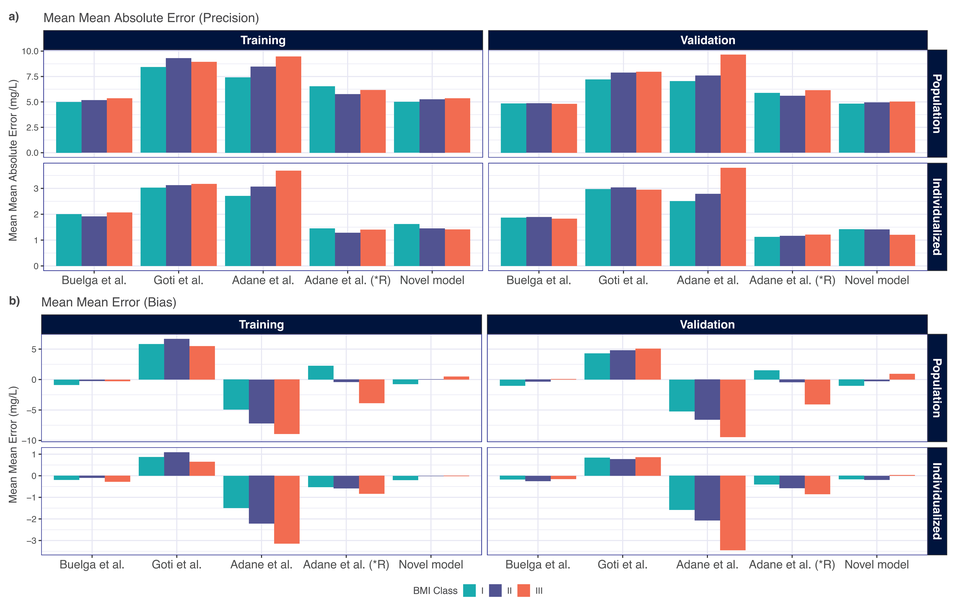
Methods

- De-identified data from N = 1717 (training set) and *N* = 1276 (validation set) courses of vancomycin administered to obese adults (BMI ≥ 30 kg/m2) from hospitals across the US, EU, and Australia were included
- The performance of the the models described by Buelga et al. (2005), Adane at al. (2015), and Goti et al. (2018) with respect to precision, bias, and variance were compared, and their predictive ability was evaluated by comparing the predicted vancomycin blood plasma concentration at the time of each recorded vancomycin assay to the model-predicted concentration
- Goodness of fit of both population and individualized models was assessed, and elastic net regression was used to identify sources of predictive error in the obese patient cohort
- A variety of body size metrics was evaluated and a novel 1-compartment model using ideal body weight (IBW) as body size metric was developed
- Performance of the novel 1-compartment model was evaluated and compared to previously published models

Results

- The obese-specific model (Adane et al.) exhibited the lowest predictive ability, the highest absolute error in the morbidly obese (BMI ≥ 40 kg/m2), as well as consistent bias across the WHO BMI classes
- Bias (calculated as mean of mean errors [MME], mean per-patient mean predictive error) unexpectedly was the highest in the obese-specific model. However, all published models showed bias across obesity classes
- Re-estimation of model parameters alone did not eliminate bias towards under-predicting concentrations in the more obese patients, with elastic net regression suggesting that existing vancomycin population models are biased in higher obesity classes due to use of total body weight (TBW) as body size estimate
- A novel 1-compartment model using IBW as body size metric exhibited the lowest bias and imprecision (-0.58 mg/L and 3.64 mg/L respectively) at predicting withheld vancomycin concentrations

Precision and Bias of Models by WHO BMI Class in the Training and Validation Data Sets



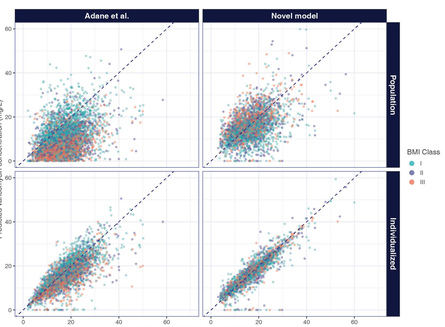
Predictive ability (R^2, percent variance explained) of population (pop) and individualized (ind) models on the training and validation data sets.

	Training		Validation	
Model	pop. R^2	ind. R^2	pop. R^2	ind. R^2
Buelga et al.	21.7%	75.5%	22.4%	77.1%
Adane et al.	13.6%	62.1%	14.1%	65.3%
Goti et al.	12.9%	65.9%	12.6%	66.9%
Adane et al. (*R)	13.0%	78.8%	13.4%	80.9%
Novel model	21.0%	80.9%	21.7%	81.8%

Notes:
- All concentration and serum creatinine assay results within each course were used to individualize each model
- Adane et al. model with parameters re-estimated using the training data set is labeled Adane et al. (*R)

Results

Observed vs Predicted Vancomycin Concentration



Demographics of Patients in the Training and Validation Data Sets

Note: Values are given as Mean (SD) for age, height, and weight; Median [IQR] for BMI

	Training			Validation		
	I	II	III	I	II	III
N	880 (523 M)	413 (236 M)	424 (205 M)	629 (362 M)	330 (167 M)	317 (153 M)
BMI, kg/m²	32.1 [31.0 - 33.4]	37.1 [35.9 - 38.4]	45.1 [42.1 - 50.0]	32.2 [31.0 - 33.5]	37.1 [36.1 - 38.2]	45.6 [42.3 - 51.7]
Age, years	62.2 (15.0)	59.6 (14.5)	58.3 (13.7)	62.7 (15.5)	60.6 (15.5)	57.8 (13.9)
Height, cm	171.4 (11.1)	171.1 (11.0)	169.0 (11.3)	171.0 (11.3)	170.3 (11.1)	169.8 (11.1)
Weight, kg	95.1 (13.1)	109.5 (14.6)	135.0 (25.1)	94.8 (13.5)	108.6 (15.0)	140.3 (30.3)

Conclusions

- Existing vancomycin population models are biased in higher obesity classes due to use of total body weight
- The novel 1-compartment model using ideal body weight as body size estimate demonstrated the highest predictive ability, while exhibiting negligible bias by obesity class
- Bayesian or model-informed precision dosing using the novel model, individualized with concentration data, was the most appropriate method evaluated for dosing vancomycin in obese patients

Disclosure: The authors of this poster disclose that they are employees of DoseMe, a commercial provider of model-informed precision dosing software.