Evaluation of population pharmacokinetic model predictive performance in adults on hemodialysis treated with vancomycin

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Background

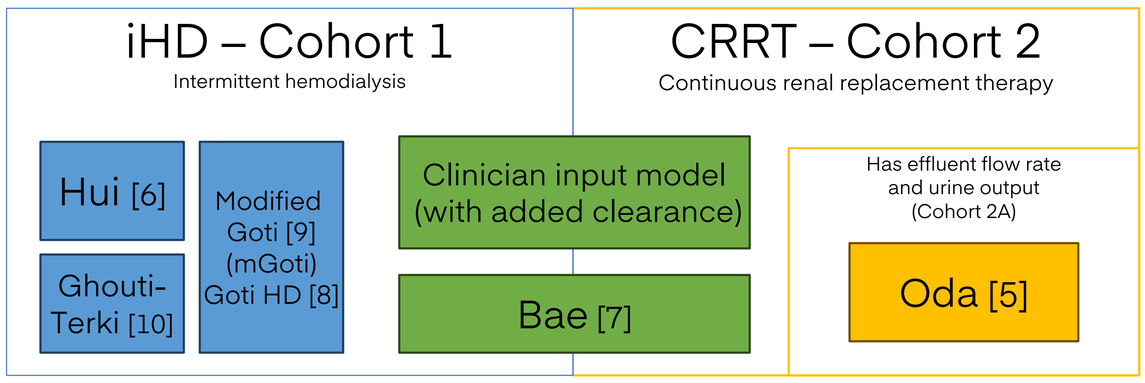
- Vancomycin is an antibiotic with a narrow therapeutic range. Achieving an area under the concentration-time curve (AUC) between 400-600 mg·h/L is crucial for therapeutic success [1-3].
- Model-informed precision dosing (MIPD) uses therapeutic drug monitoring (TDM) to inform population pharmacokinetic (popPK) models to guide dosing decisions [4].
- The PK of vancomycin in patients undergoing hemodialysis (HD) is significantly influenced by both the HD process and the underlying physiological changes that necessitated HD.
- The effectiveness of MIPD tools for optimizing vancomycin dosing and exposure at the bedside depends on the predictive performance of popPK models for hemodialysis patients.
- No large-scale evaluation of published popPK models has yet been conducted.

Objective

Evaluate predictive performance of popPK models for adult patients undergoing hemodialysis treated with vancomycin.

Methods – Data and Models

- De-identified routine clinical care data entered into the InsightRX Nova MIPD platform between June 6, 2015 and March 30, 2025 were retrospectively analyzed
- Patients with 1+ TDM sample, 1+ vancomycin doses, and hemodialysis during some or all of their treatment course were included.



- Six popPK models were judged as fit for purpose and included.
- Predictions were made iteratively using PKPDsim [11], where data up to and including the first N samples were used to predict the $(N+1)^{th}$ sample.

Model development population characteristic	Oda	Goti HD	Hui	Bae	Ghouti-Terki
Covariates	RUO: reduced urine output EFR: effluent flow rate	Creatinine clearance (CRCL), hemodialysis (HD)	HD	CRCL, CRRT	IHD, CRRT
Site Location	Japan	USA	Australia	Korea	France
# Patients	17	1812	48	220	16
# TDMs	80	2765	180	1020	224
Hemodialysis	0	336	48	9	280 sessions
CRRT	17	0	0	20	0
Age (y)	64 (19-92)	57 (17-101)	61.5 (23-86)	63 (21-98)	68.5 (36-91)
Serum creatinine (mg/dL)	1.7 (0.4-7.0)	1.3 (0.2-16.6)	7.3 (2.5-13.3)	1.7 (0.2-13.3)	NA
Weight (kg)	59.7 (43.1-117)	79 (33-255)	78 (40-226)	61.6 (30.0-127)	77 (39-126)

Methods – Performance Metrics

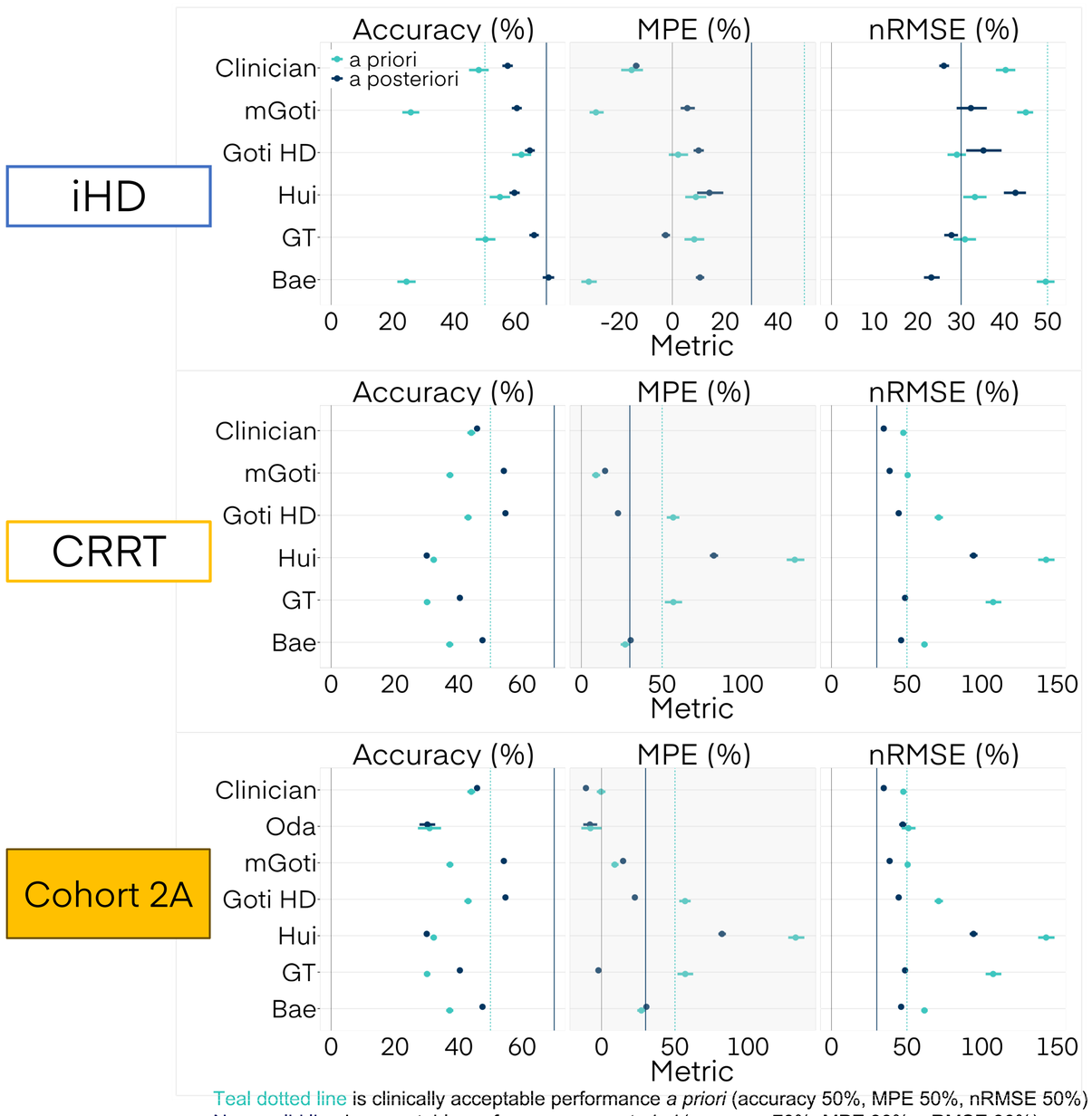
For i^{th} observation (obs) and prediction (pred) pair with N observations:

- Accuracy: prediction within 2.5 mg/L or 20% of observation
- Mean percent error: $MPE = \frac{1}{N}\sum_{i=1}^{N}\frac{pred_i - obs_i}{obs_i} \times 100\%$
- Normalized root mean square error: $nRMSE = \sqrt{\frac{\sum_{i=1}^{N}(pred_i - obs_i)^2}{obs_i \times N}}$

Results

Characteristic	Count or Median (Min-Max)
# Patients	1246
# Treatment Courses	1663
# of TDMs	5084
Age (y)	60.4 (17.8-101.6)
Weight (kg)	91.9 (37.2-360.7)
Height (cm)	167.6 (55-210.8)
Serum Creatinine (mg/dL)	2.1 (0.28-26.7)
Sex (female/male)	461/785

- 108 patients undergoing iHD and 1138 patients undergoing CRRT from 81 U.S.-based partner hospital systems were included.



Conclusions

- **No models met all performance thresholds for acceptable clinical performance.**
- Models developed on larger, multi-center data sets generally outperformed more niche models.
- Use of more detailed HD information (like in the Oda model) does not necessarily improve predictive performance.
- iHD patients were generally better modeled than CRRT patients in this data.
- Future work should focus on using large data sets to fit models on time-varying HD covariates.

References

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