One model to rule them all?

Optimal model for model-informed precision dosing of vancomycin varies across healthcare providers

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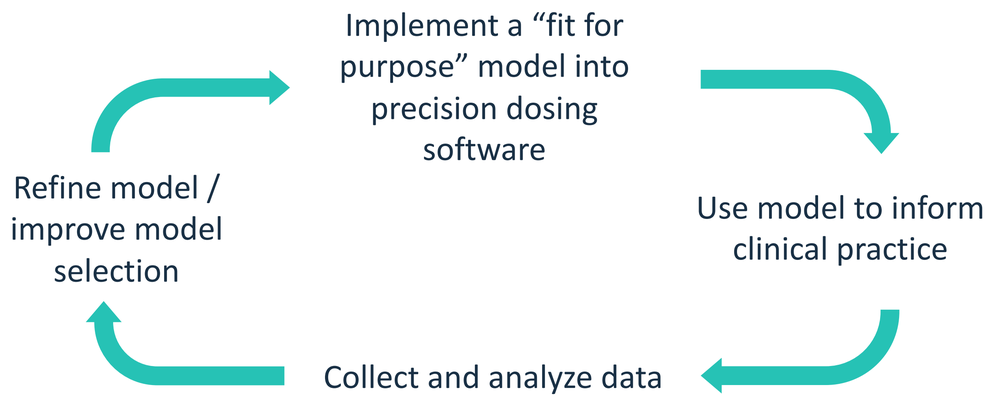
Background: AUC-guided dosing of vancomycin

- Infectious Diseases Society of America's recommends AUC-based dosing for vancomycin[1]
- Model-informed precision dosing (MIPD) software facilitates AUC estimation, and is increasingly used at the point-of-care[2]
- MIPD requires an adequately predictive model[3]
- Exposure target attainment early in therapy, linked to improved patient outcomes[4], could be improved by using population pharmacokinetic (popPK) model-based selection of initial doses.
- Existing meta-analyses of model predictive performance were based on a limited number of patients at 1-2 institutions[5-8]



Objectives

- Which PK model has the best accuracy for model-informed precision dosing of vancomycin in adult patients?
- **Do models perform the same across healthcare organizations?**

Methods: Data source

De-identified, retrospectively analyzed routine clinical care data of adults (> 18 years) treated with vancomycin.

- At least 2 doses of vancomycin
- At least 1 serum level collected

Property	Count
# Patients	170,838
# Healthcare Institutions	80
# drug levels	349,436

Methods: PK modeling

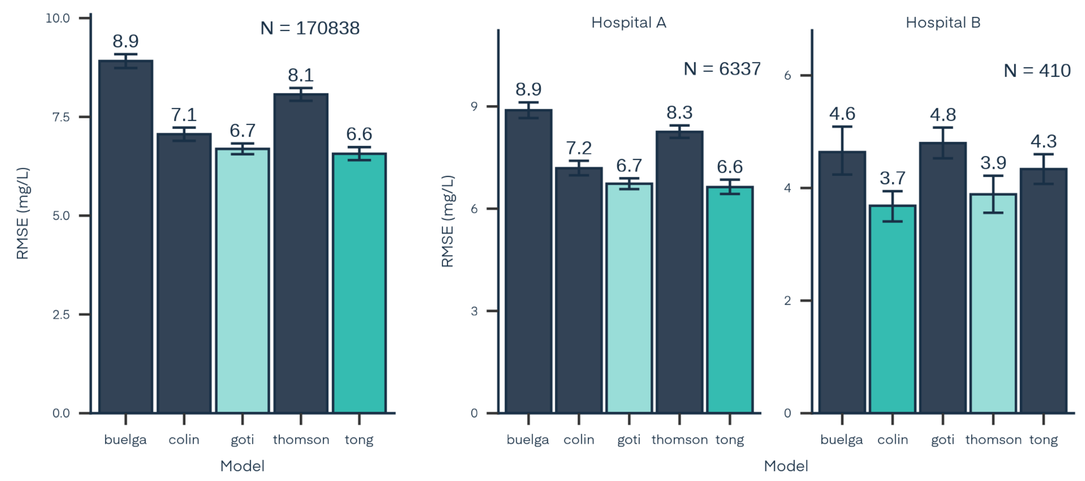
Property	Buelga[8]	Colin[9]	Goti[10]	Thomson[11]	Tong[12]
Development data set # Patients (#TDMs)	215 (1004)	2554 (8300)	1812 (2765)	398 (1557)	1812 (2765)
Model structure	1-cmt	2-cmt	2-cmt	2-cmt	2-cmt
Covariates	WT, CRCL	WT, AGE, CR	WT, CRCL	WT, CRCL	WT, CRCL

- Pragmatic literature search
- Use population covariates to predict first level (*a priori*)
- Evaluate prediction imprecision: root mean square error

References

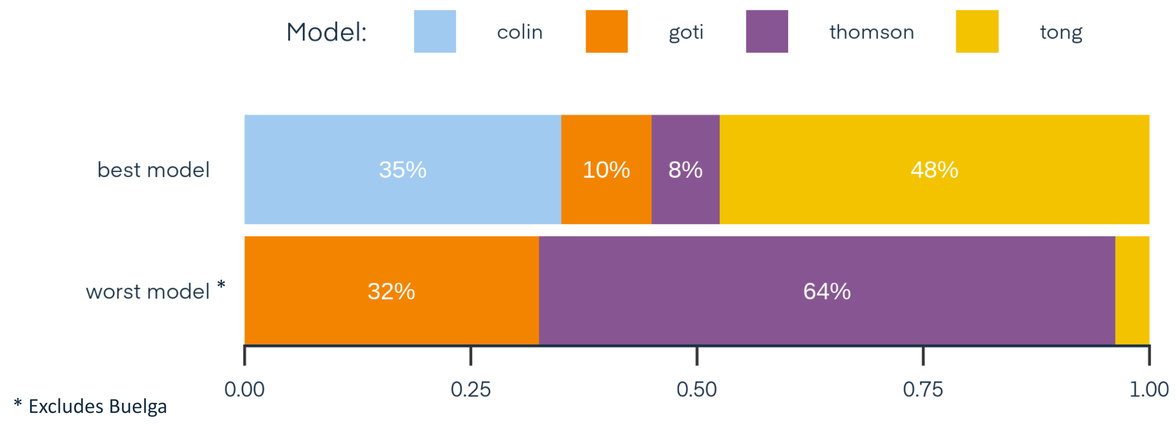
1. Rybak, et al. J.Pediatric.Infect.Dis 2020
2. Keizer et al., ACOP 2022
3. Keizer et al. CPT:PSP 2018
4. Al Sulaiman, et al. BMC Infect.Dis 2021
5. Guo et al. AAC 2019
6. Broeker et al. Clin.Microb & Infect 2019
7. Smit et al. BJCP 2020
8. Buelga et al. AAC 2005
9. Colin et al. Clin.Pharmacokin. 2019
10. Goti et al. TDM 2018
11. Thomson et al. JAC 2009
12. Tong et al. TDM 2021

Results: Variation in model accuracy across healthcare sites



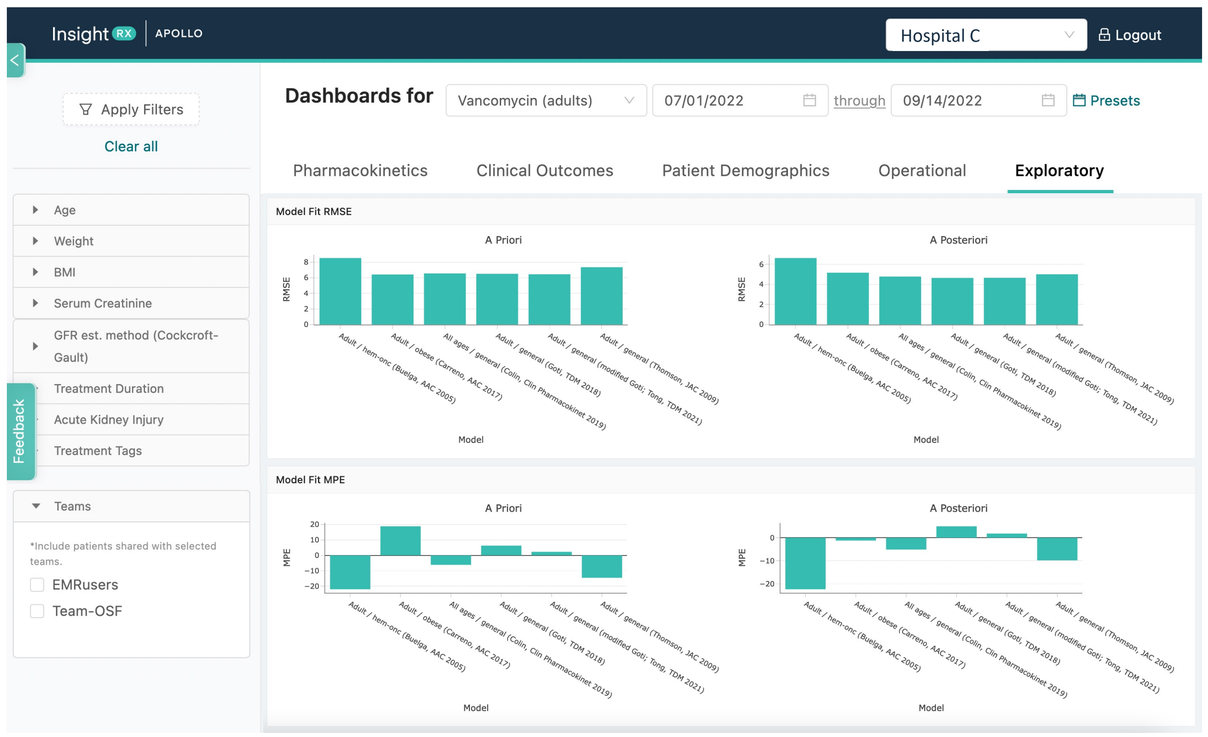
Dark turquoise bar: lowest RMSE. Light turquoise bar: statistically tied with lowest bar (overlapping 95% confidence intervals).

- Aggregating prediction imprecision across all healthcare institutions suggests the **Tong** model performs best in adult patients.
- Aggregating imprecision across individual institutions (N = 80) suggests the ”best” model is only best in **48%** of institutions, and *worst* in 4%.



* Excludes Buelga

Recommendation: Tailor practices to your institution



Conclusion

- Best model for a MIPD population varies from site to site
- Underlying causes unclear:
  - demographics (e.g.: age, comorbidities)
  - operational (e.g.: assay used, sampling times)
  - institution type (e.g.: critically ill patients, community hospitals)
- Be cautious when interpreting meta-analyses conducted at only a handful of institutions, on smaller patient data sets.
- Tailor models to MIPD population