Vancomycin PK & InsightRx Refresher

Molly Miller, PharmD, BCIDP

Clinical Pharmacist Practitioner, Infectious Diseases/Antimicrobial Stewardship

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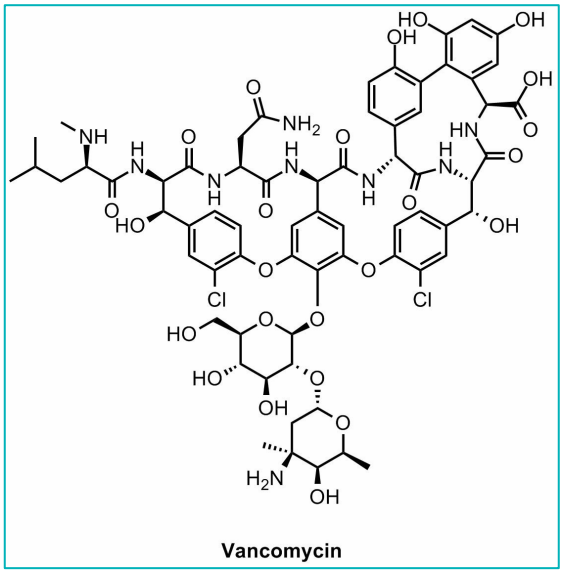
Nebraska Medicine

Vancomycin Overview

- Background
- Pharmacokinetics
- Indications/Spectrum
- Toxicity/Side Effects
- Dosing/Monitoring

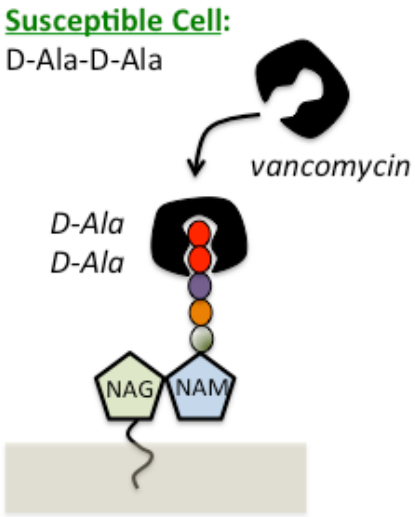
Vancomycin: Background

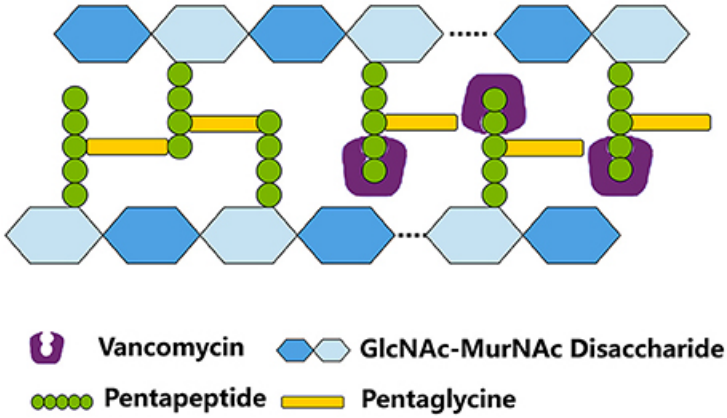
Tricyclic glycopeptide antibiotic



Blocks peptidoglycan polymerization in bacterial cell wall → **inhibits cell wall synthesis**

- **Concentration-dependent**
- **Slowly** bactericidal





Tulane School of Medicine. *Glycopeptide Pharmacology.*
Hu Q et al. *Front Microbiol.* 13 October 2016
https://www.gesundheitsindustrie-bw.de/en/article/news/p450-catalysed-glycopeptide-biosynthesis

Vancomycin: Pharmacokinetics

Distribution

- Distributes to most compartments (blood, lungs, skin)
- CNS penetration enhanced with inflamed meninges
- V_d ~ 0.7 L/kg

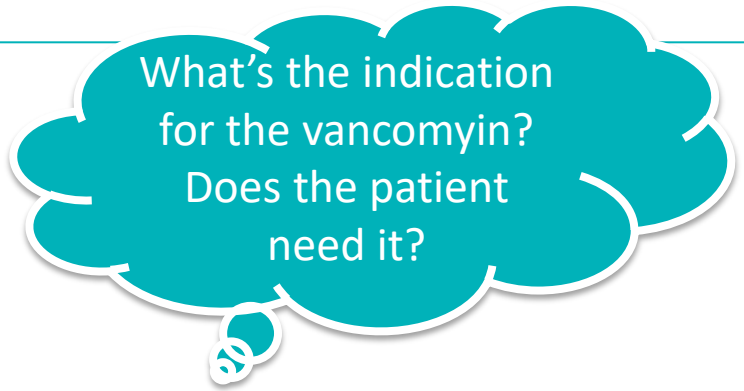
Elimination

- Excreted primarily via kidneys, clearance ~ CrCl
- $t_{1/2}$ ~ 6-7 hrs with normal renal function, prolonged in renal insufficiency

Vancomycin: Indications/Spectrum

Treatment of severe infections caused by gram-positive organisms

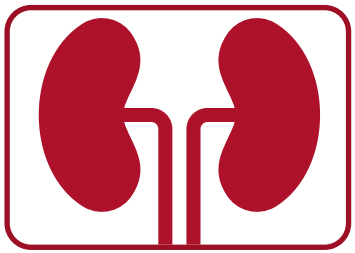
- MRSA
- Ampicillin-resistant enterococcal infections
- Beta-lactam-susceptible gram-positive pathogens in patients with severe beta-lactam allergy



Vancomycin: Toxicity/Side Effects

Infusion Reaction

- Histamine reaction causing redness, flushing, itching
- Slow down infusion (double duration), can give diphenhydramine



Nephrotoxicity

- Incidence 5-43%
- Risk factors: **trough >15, AUC >563,** doses >4 g/day, concomitant nephrotoxins, duration >4 days, weight >100 kg
- Usually reversible

Ototoxicity

- 2% incidence, more common in elderly
- Vestibular and/or cochlear damage → sensory hearing loss/tinnitus
- Reversible

Van Hal et al. *Antimicrob Agents Chemother.* 2013;57(2):734-744
Chavada et al. *Antimicrob Agents Chemother*. 2017; 61(5)
Pai MP *Adv Drug Deliv Rev.* 2014
Forouzesh A. Antimicrob Agent Chemother. 2009

Risk of AKI with Therapeutic AUC

Note: linear increase in probability of AKI throughout "therapeutic" AUC range; lower is better

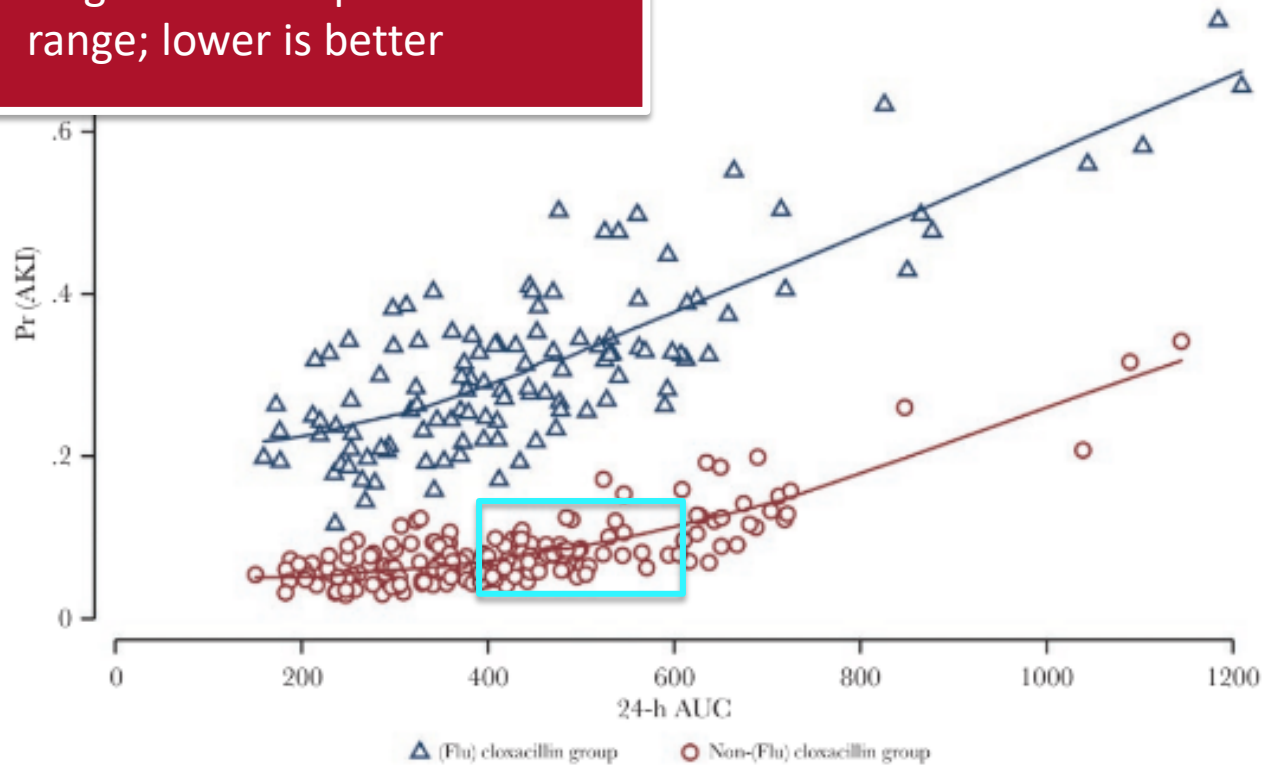
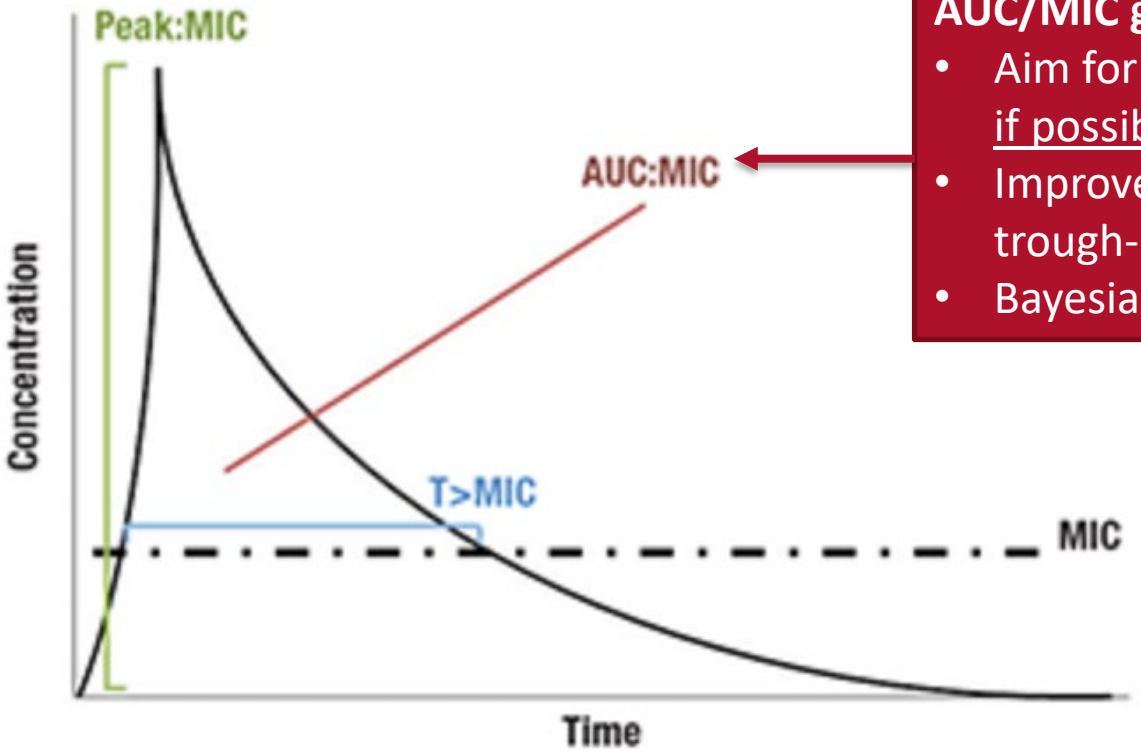


Figure 1. Day 2 vancomycin exposure–toxicity relationships (stratified by (flu)cloxacillin vs non-(flu)cloxacillin groups). Pr(AKI), probability of Stage 1 AKI as defined by modified KDIGO per the parent study (ie, CAMERA2): Stage 1 is serum creatinine 1.5–1.9 times baseline in the first 7 days (OR ≥26.5 μmol/L increase from baseline in the first 48 hours); Stage 2 is serum creatinine 2.0–2.9 times baseline in the first 7 days; Stage 3 is serum creatinine ≥3.0 times baseline in the first 7 days (OR ≥353.6 μmol/L

Liu et al. OFID 2021.

Vancomycin: Dosing/Monitoring



AUC/MIC goal 400-600 mg*hr/L

- Aim for AUC24 400-500 mg*hr/L if possible
- Improved efficacy, reduced toxicity vs trough-based monitoring
- Bayesian method preferred

Assume MIC = 1

- >90% MRSA isolates have MIC ≤1 mg/L
- Variability in MIC measurement ±1 dilution; difference between methods used
- Recent meta-analysis showed no increase in mortality with MIC >1.5 vs <1.5 mg/L
- Base therapy decisions on clinical response

Kalil et al. *JAMA*. 2014; 312(15):1552-1564

Vancomycin: Dosing/Monitoring

Loading Dose

- 20-30 mg/kg may be considered in critically ill patients to achieve PK/PD targets sooner (cap at 2g per dose)
- Not proven to improve outcomes, but also does not increase risk of nephrotoxicity
- Not routinely needed in floor patients

Maintenance Dose

- Usual dose range ~10-15 mg/kg q12-24h
- Utilize InsightRx to target AUC 400-600 unless patient is requiring dialysis

*Dosing weight typically actual body weight or adjusted body weight, if obese

Vancomycin: Dosing/Monitoring

Generally wait to order trough until vancomycin at steady state and confirmed to be continued

Can be obtained earlier or at alternative sampling time (i.e., peak or random level) in patients with severe infection/fluctuating renal function, morbidly obese patients, or in patients for whom Bayesian models do not provide good fit

Usual sampling times (but **do not** re-draw trough if not drawn at correct time)*

- Trough: ≤ 30 min prior to infusion (usual target range 10-15 mg/L)
- Peak (if ordered): 1 hr after infusion ends (usual target 25-40 mg/L)

*If level drawn during infusion, use clinical judgement as these are often inaccurate; would probably exclude and re-draw in this case

Case!

A 60 YOM with a hx of DM, ETOH use, s/p R BKA for chronic non-healing ulcers presents with subacute R index finger swelling and erythema. On exam the patient has extensive soft tissue swelling and X-ray reports possible foci of soft tissue gas.

Additional patient information
Weight: 114 kg
Height: 180 cm
BMI: 35.2
Baseline labs: BG 88 | Na 145 | K 3.6 | Scr 0.9 | INR 1.0 | Hgb 12.1 | Plt 260

1. What initial vancomycin maintenance dose do you start this patient on?
   a. 1250 mg q12h
   b. 750 mg q8h
   c. 1750 mg q12h
   d. 3000 mg q24h

How do we choose empiric dosing?

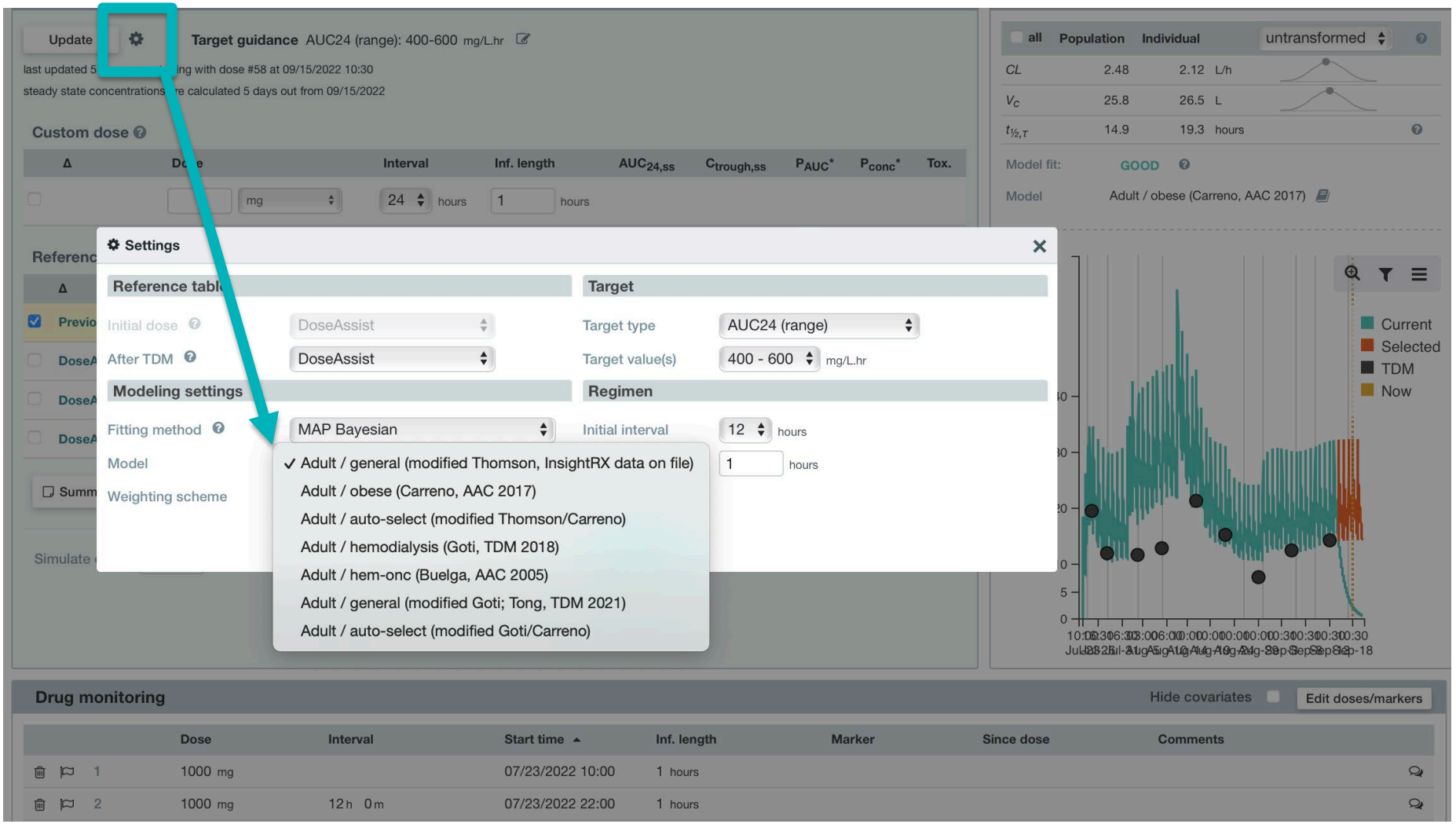
InsightRx: Initial Model Selection

Patient Characteristics	Model Selection
General patient population	• All ages/general: **Colin**, Clin Pharmacokinet 2019 • Adult/general: modified **Thomson**, InsightRx data on file) • **Adult/auto-select**: modified Thomson/Carreno*
Obese (BMI > 30-40) • InsightRx recommends also referencing other models	• Adult/obese (**Carreno**, AAC 2017) • Validated in BMI > 40, yet the model also performs well for BMI >30
Fluctuating renal function • Concern for slower vancomycin clearance (consider second level)	• Adult/general: modified **Goti; Tong,** TDM 2021 • Adult/auto-select: modified Goti/Carreno*

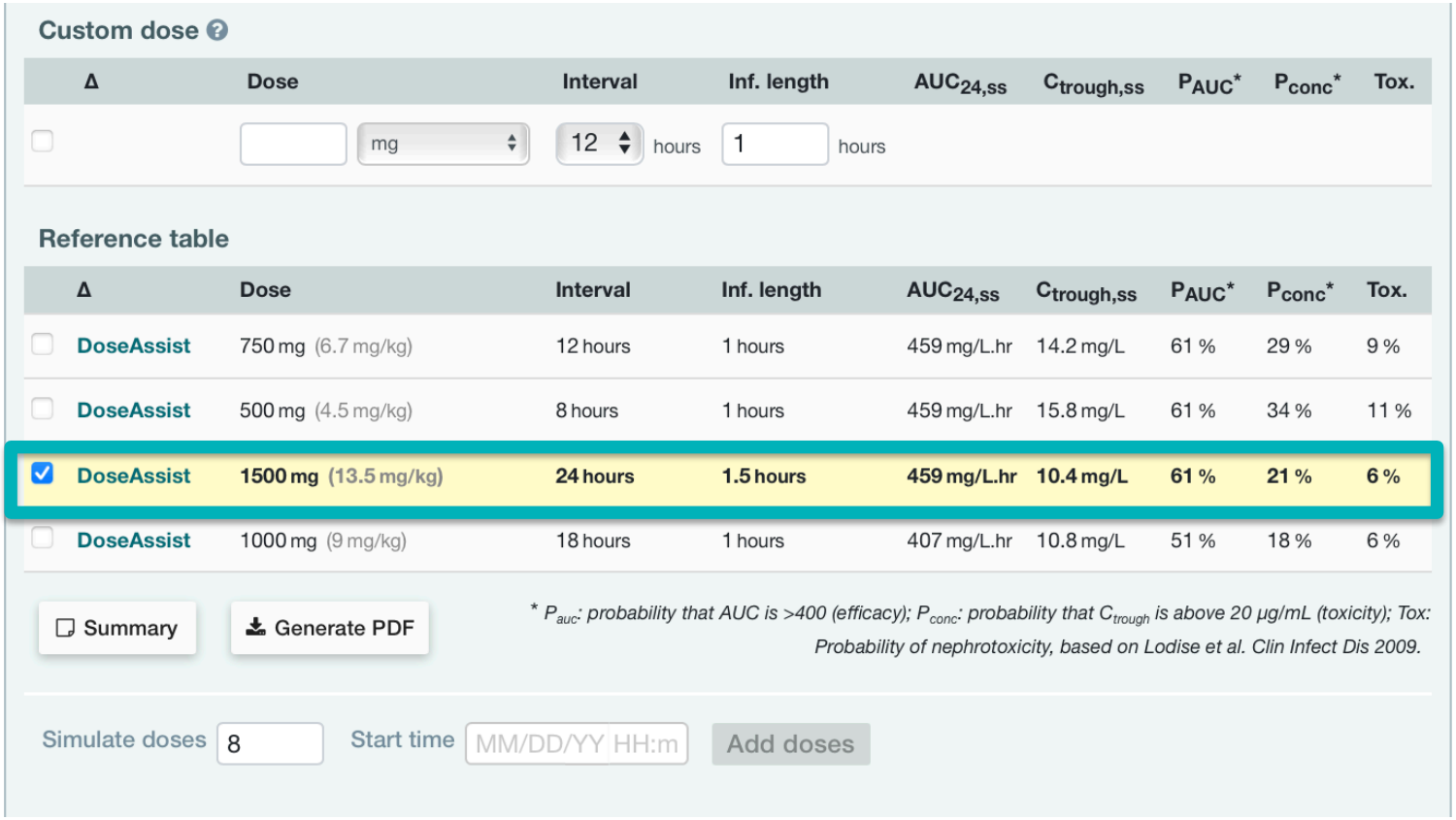
Tip: If unsure of which model to choose empirically, check multiple models based on your patient's characteristics

*note, the "auto-select" options use Carreno when BMI >40; otherwise, will default to the standard model

InsightRx: Model Selection



InsightRx: Selecting an Initial Regimen



Custom dose

Δ	Dose	Interval	Inf. length	$AUC_{24,ss}$	$C_{trough,ss}$	P_{AUC}*	P_{conc}*	Tox.
☐	mg	12 hours	1 hours					

Reference table

Δ	Dose	Interval	Inf. length	$AUC_{24,ss}$	$C_{trough,ss}$	P_{AUC}*	P_{conc}*	Tox.
☐ DoseAssist	750 mg (6.7 mg/kg)	12 hours	1 hours	459 mg/L.hr	14.2 mg/L	61 %	29 %	9 %
☐ DoseAssist	500 mg (4.5 mg/kg)	8 hours	1 hours	459 mg/L.hr	15.8 mg/L	61 %	34 %	11 %
☑ **DoseAssist**	**1500 mg (13.5 mg/kg)**	**24 hours**	**1.5 hours**	**459 mg/L.hr**	**10.4 mg/L**	**61 %**	**21 %**	**6 %**
☐ DoseAssist	1000 mg (9 mg/kg)	18 hours	1 hours	407 mg/L.hr	10.8 mg/L	51 %	18 %	6 %

Summary | Generate PDF

* P_{auc}: probability that AUC is >400 (efficacy); P_{conc}: probability that C_{trough} is above 20 µg/mL (toxicity); Tox: Probability of nephrotoxicity, based on Lodise et al. Clin Infect Dis 2009.

Simulate doses 8 | Start time MM/DD/YY HH:m | Add doses

Tip: When choosing a regimen, calculate the total daily dose of vancomycin. Are you able to give this amount at a less frequent interval?

Case!

A 59 YOM with a hx of DM, ETOH use, s/p R BKA for chronic non-healing ulcers presents with subacute R index finger swelling and erythema. On exam the patient has extensive soft tissue swelling and X-ray reports possible foci of soft tissue gas.

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1. What initial vancomycin maintenance dose do you start this patient on?
   a. 1250 mg q12h
   b. 750 mg q8h
   c. 1750 mg q12h
   d. 3000 mg q24h

Case Continued

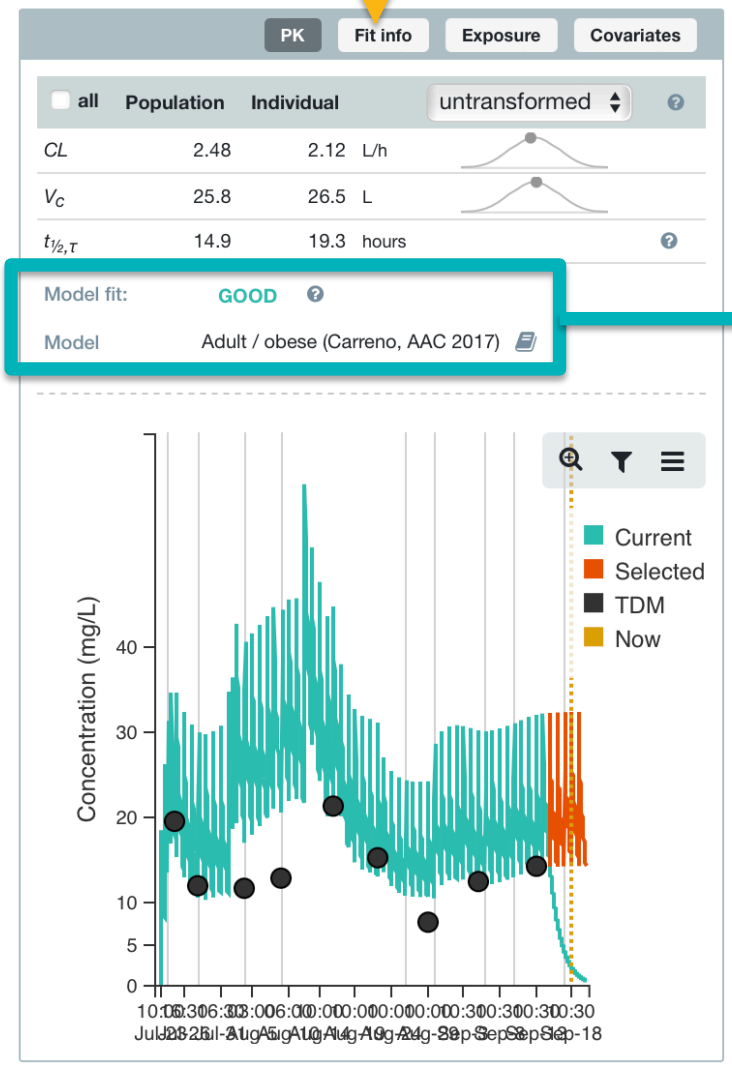
Ortho is consulted and he is taken to the OR. He is found to have significant tendon and tissue necrosis consistent with flexor tenosynovitis and osteomyelitis of the distal phalanx. Patient underwent distal interphalangeal amputation. Intraoperative cultures grow 1+ coagulase-negative staphylococcus and 1+ MRSA. Vancomycin MIC is 1 mg/L. Blood cultures are negative.

The following levels are obtained at steady state while he is on vancomycin 1750 mg every 12 hr, with each infusion given over 2 hr
Last dose of vancomycin given at 0500 and completed at 0700
Peak level 30.4 mg/L at 0900 (2 hours after completion of dose)
Trough level 14.6 mg/L at 1800 (13 hours after dose)
SCr remains stable at 0.9 mg/dL

2. What dose of vancomycin is most appropriate based on these findings?
    a. Continue 1750 mg q12h
    b. 750 mg q8h
    c. 1500 mg q12h
    d. 1250 mg q12h

InsightRx: Model Fit

Tip: Check the Fit info tab to see how well this model is predicting your patient's levels



Model Fit

- **Good**
  - All provided data fits well into InsightRx's calculations and predictions
  - Should generally be considered reliable
- **Intermediate**
  - Provided data does not fit as well into InsightRx's calculations
  - Predictions may be less reliable
- **Poor**
  - Provided data is highly inconsistent and unable to be fit together well
  - Predictions should not be considered reliable

InsightRx: Model Fit

PK | Fit info | Exposure | Covariates

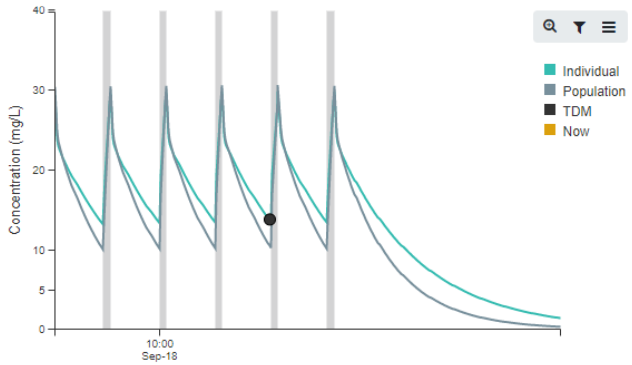
Time	TDM	Prediction	Weight	Fit
08/12/2022 20:00	11.4	7.23 mg/L	0%	
08/18/2022 19:35	18.4	15.08 mg/L	0%	
08/22/2022 10:45	9.2	7.95 mg/L	0%	
09/13/2022 16:30	6.4	6.23 mg/L	26%	✓
09/19/2022 09:40	13.7	13.62 mg/L	100%	✓

Model fit: GOOD

Model: Adult / obese (Carreno, AAC 2017)

Fitting method: MAP Bayesian

Weighting scheme: Linear gradient



PK | Fit info | Exposure | Covariates

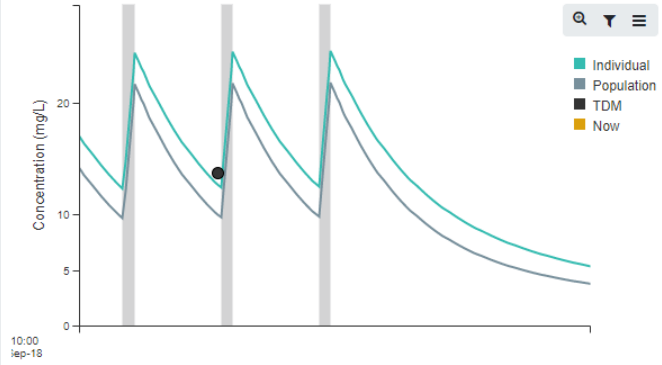
Time	TDM	Prediction	Weight	Fit
08/12/2022 20:00	11.4	11.52 mg/L	0%	
08/18/2022 19:35	18.4	13.19 mg/L	0%	
08/22/2022 10:45	9.2	7.52 mg/L	0%	
09/13/2022 16:30	6.4	5.87 mg/L	26%	✓
09/19/2022 09:40	13.7	12.65 mg/L	100%	✓

GOOD

Adult / general (modified Thomson, InsightRX data on file)

Fitting method: MAP Bayesian

Weighting scheme: Linear gradient



PK | Fit info | Exposure | Covariates

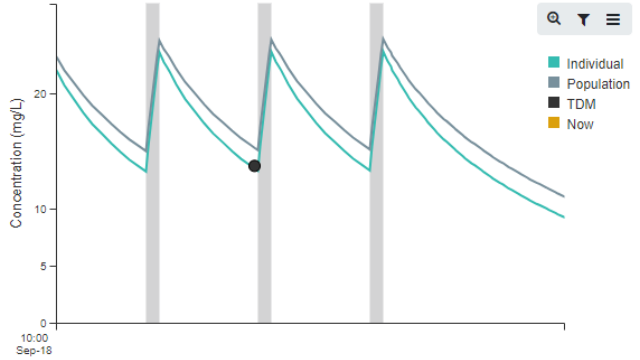
Time	TDM	Prediction	Weight	Fit
08/12/2022 20:00	11.4	12.95 mg/L	0%	
08/18/2022 19:35	18.4	13.75 mg/L	0%	
08/22/2022 10:45	9.2	7.03 mg/L	0%	
09/13/2022 16:30	6.4	7.08 mg/L	26%	✓
09/19/2022 09:40	13.7	13.46 mg/L	100%	✓

Model fit: GOOD

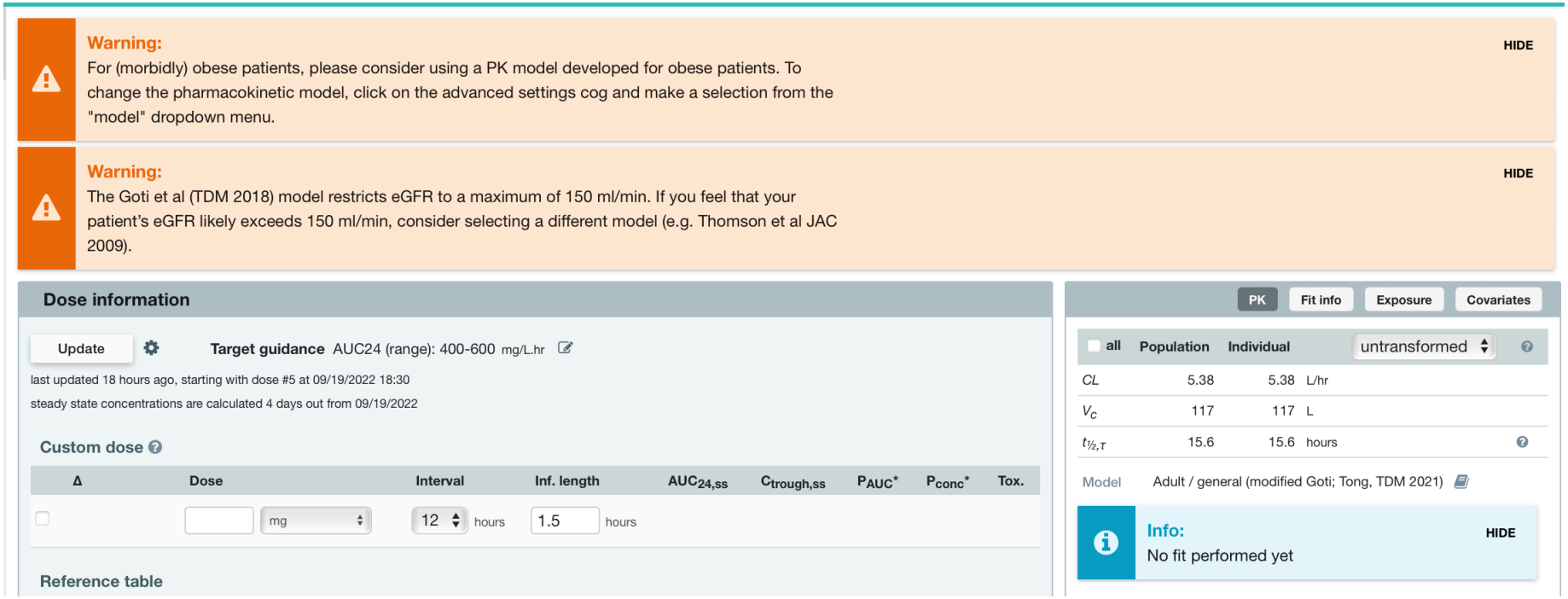
Model: Adult / general (modified Goti; Tong, TDM 2021)

Fitting method: MAP Bayesian

Weighting scheme: Linear gradient



InsightRx: Warnings



Tip: This may be an opportunity to trial the different models to see if one has a better fit

InsightRx: Tips on Finding the Right Model

Once you have a level, check the **Fit Info** tab

Is your patient clearing slower than the model you have chosen predicted?

- Try modified Goti; Tong, TDM 2021 or Goti, TDM 2018*

Is your patient clearing faster than the model you have chosen predicted?

- If using modified Goti; Tong, TDM 2021, try modified Thomson or Colin
- If using Colin or modified Thomson, try Buelga

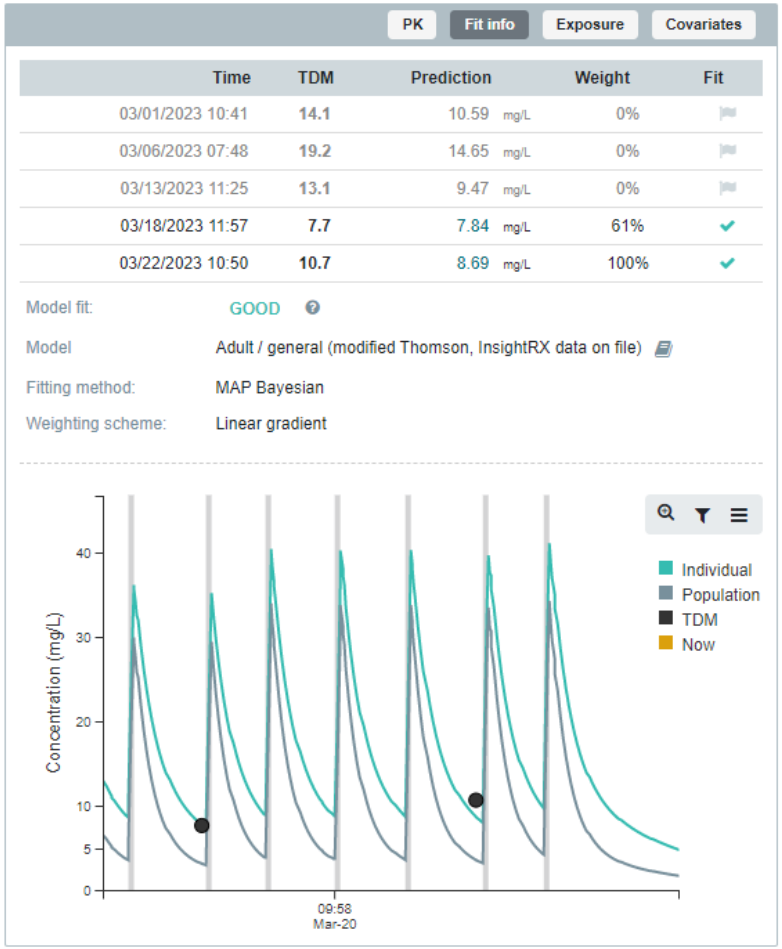
Is your chosen model not predicting well in an obese patient (BMI 30+)?

- If not using the Carreno model, try this one

If none of the models fit, try getting a level at an alternative sampling time

*reserve Goti, TDM 2018 for patients clearing slower than modified Goti; Tong, TDM 2021

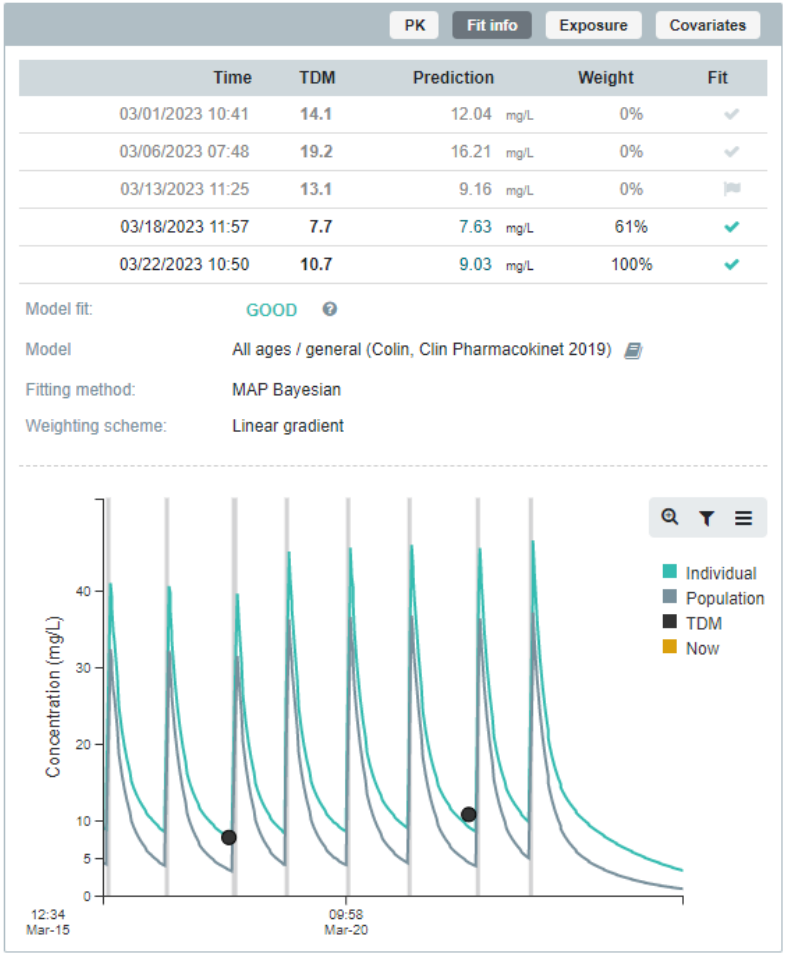
Example: Model Fit



Things to note:

- Modified Thomson model (typical default)
- Level is plotted off of the graph
- Individual and Population PK models are not in very close agreement
- Level predicted is 8.69 compared to 10.7 (~2 mg/L off)
- Could try other “default” model (Colin) to see if this is a better fit
  - Some InsightRx data suggests Colin may be a better fit for our patients

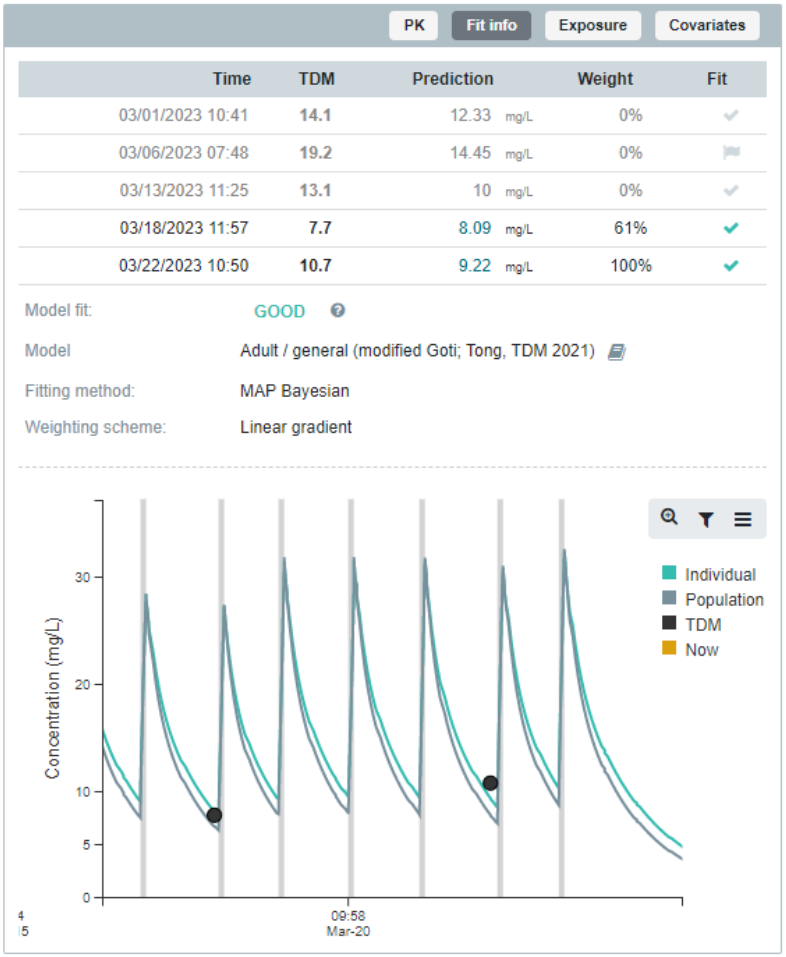
Example: Model Fit



Things to note:

- Colin model (new default)
- Level is plotted off of the graph
- Individual and Population PK models are not in very close agreement
- Level predicted is 9.03 compared to 10.7 (still ~2 mg/L off)
- Notice the pattern: in both of these “default” models, the patient’s clearance of vancomycin is slower than predicted
- Try modified Goti; Tong, TDM 2021

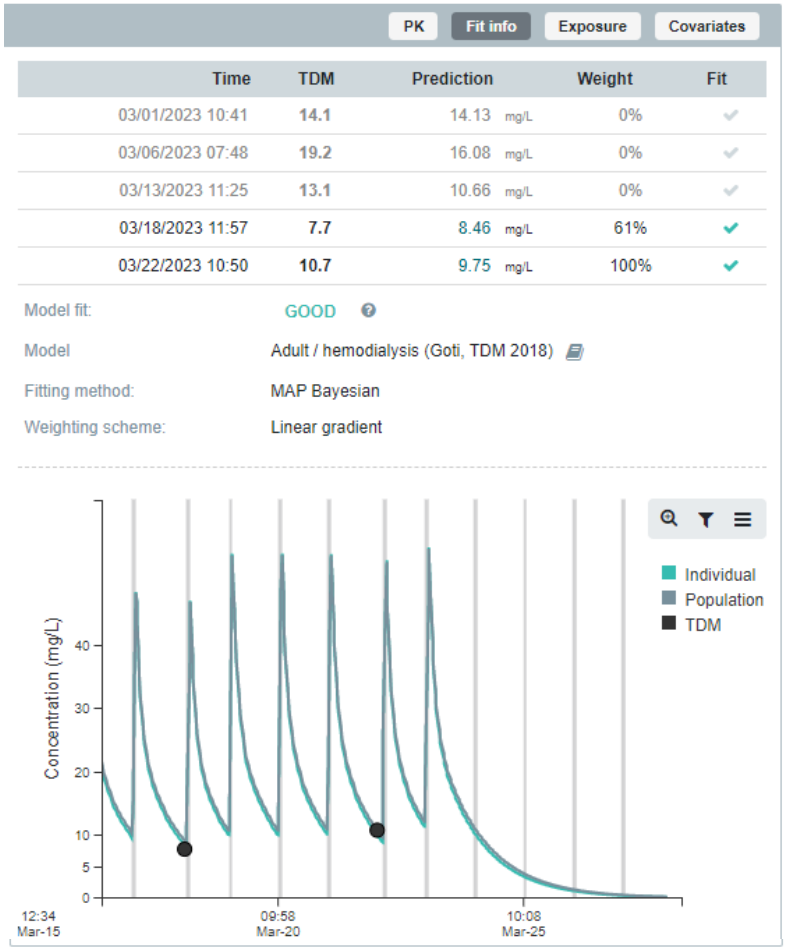
Example: Model Fit



Things to note:

- Modified Goti; Tong, TDM 2021 model
- Level is still plotted off of the graph
- Individual and Population PK models are in closer agreement, but still some room for improvement
- Level predicted is 9.22 compared to 10.7 (~1.5 mg/L off; closer, but still not great)
- Since patient is still clearing slower than this model predicts, try Goti, TDM 2018

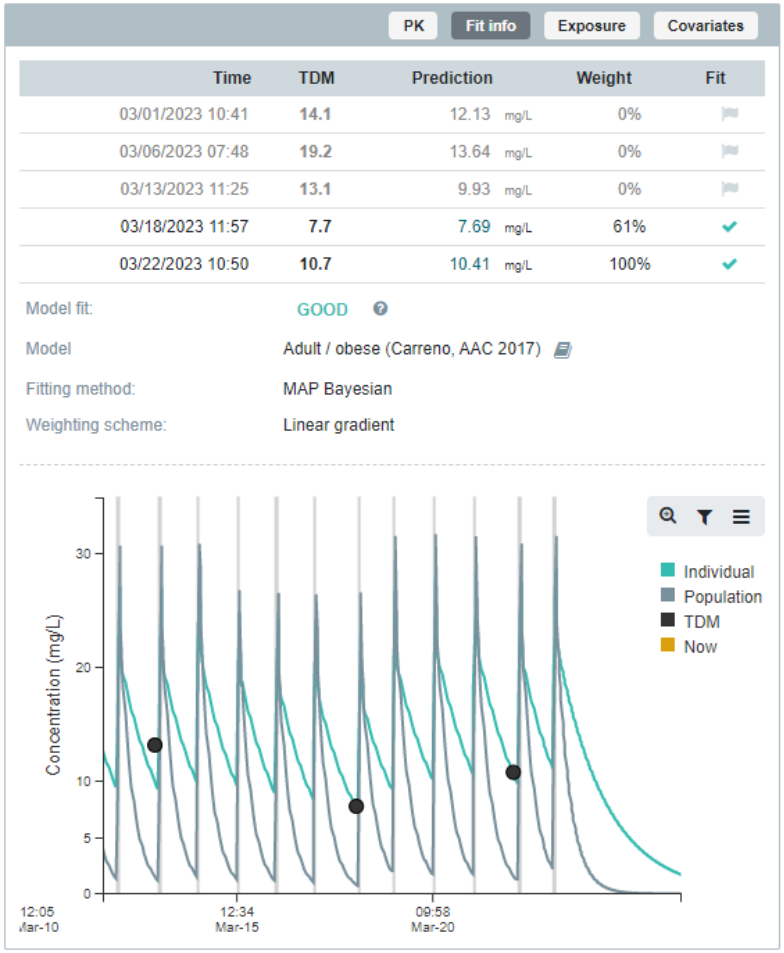
Example: Model Fit



Things to note:

- Goti, TDM 2018 model
- Level is plotted on the graph
- Individual and Population PK models are in very close agreement (basically overlapping)
- Level predicted is 9.75 compared to 10.7 (within 1 mg/L)
- This model seems to be best fit available, would proceed using this model

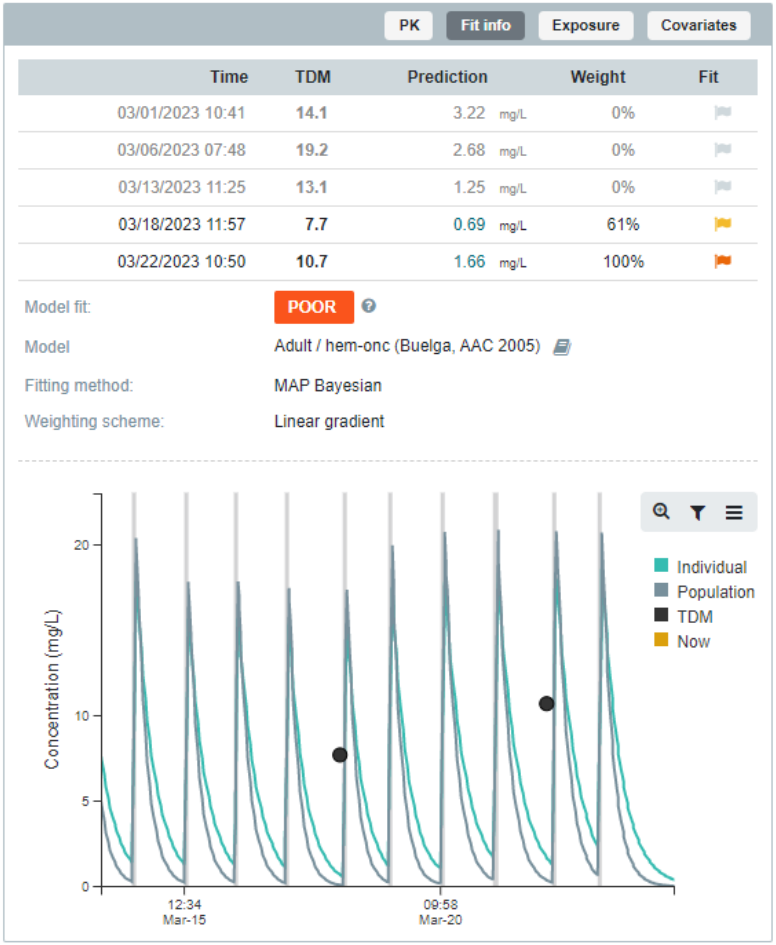
Example: Model Fit



Just for fun…

- This patient is not morbidly obese, but occasionally patients with higher BMIs (30-40) can fit the Carreno model
- In this case, this is not a good fit; though the predictions seem close, since the patient does not have a BMI>40 and graph looks wonky, would not trust this model

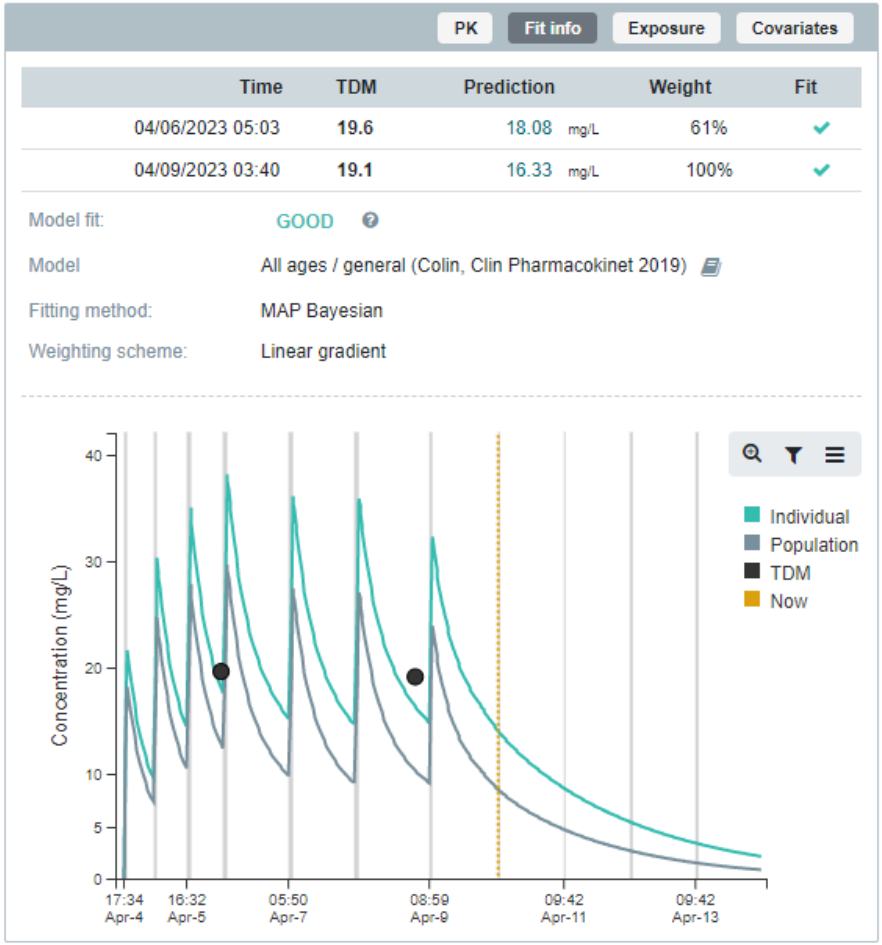
Example: Model Fit



Another just for fun:

- The Buelga model is typically for patients with faster clearance
- This patient demonstrated the opposite kinetics based on our initial models, so would not expect this model to fit
- As you can see, this model is clearly a poor fit for this patient

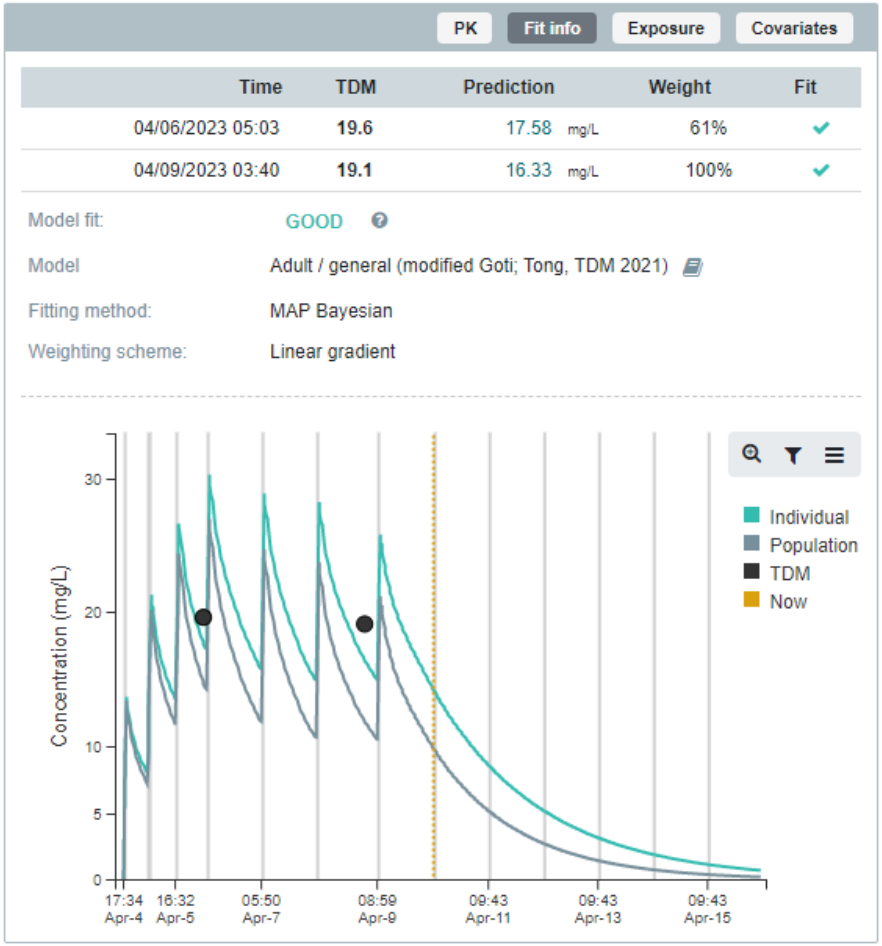
Another Example



- 70 YOM, SCr 1.15 (CrCl~79), BMI 29
- You open InsightRx and see this

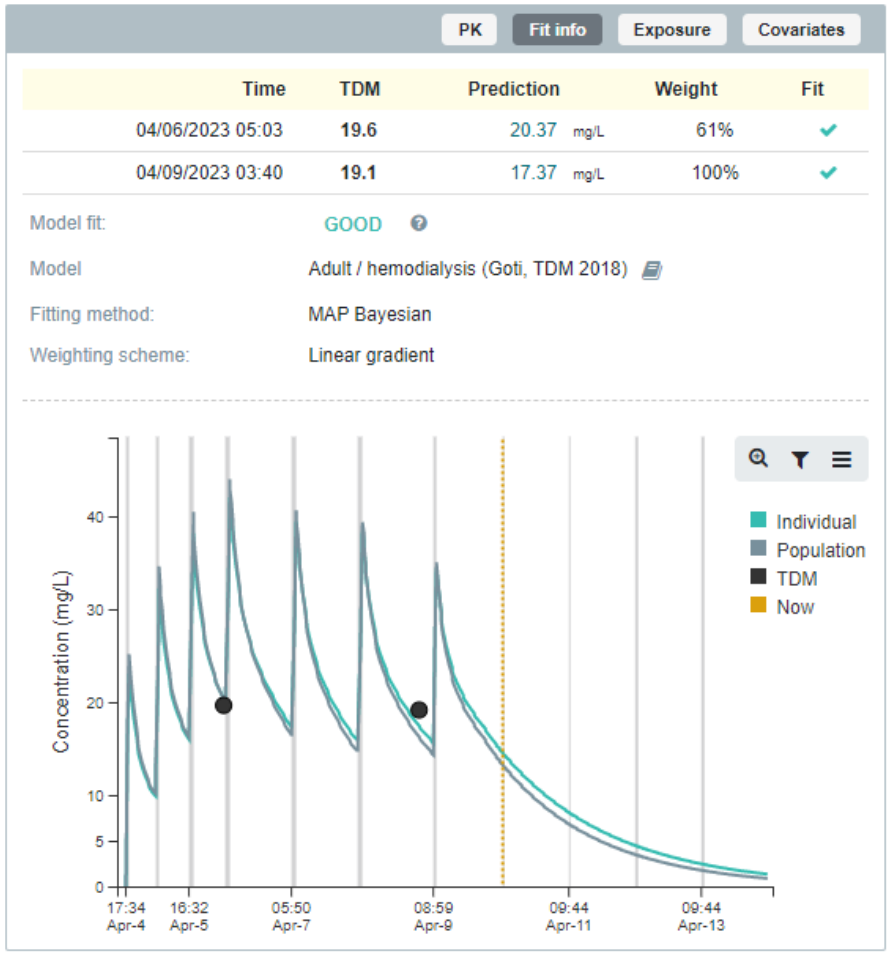
- Is this model a good fit? Which other might you try?

Another Example



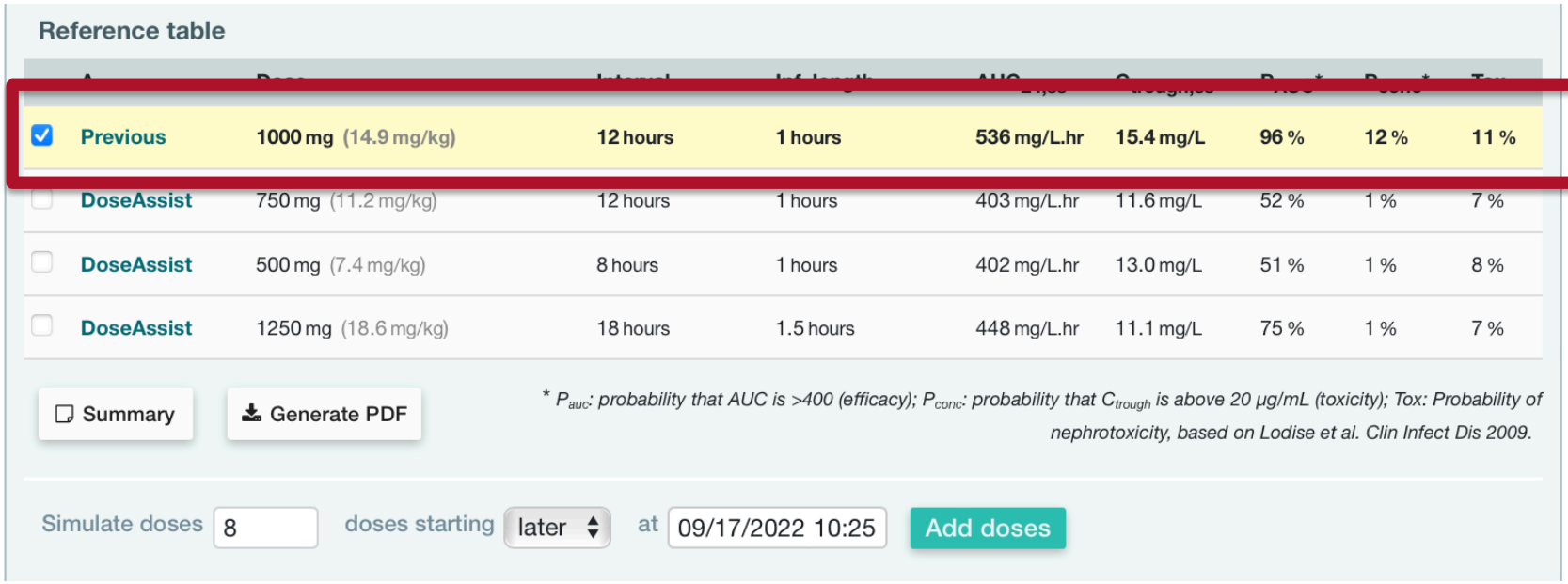
- As the “default” Colin model was not a good fit, and patient appears to be clearing vancomycin slower than predicted, try modified Goti; Tong, TDM 2021 to see if it’s a better fit
- As you can see, this model is still not a great fit; which model might you try now?

Another Example



- In this case, the Goti, TDM 2018 model is a much better fit; use this model for this patient
  - Note that the prediction is still a little off, even with the “best fitting” model; here, you may consider getting a level at an alternative sampling time and/or consulting ASP to consider flattening priors

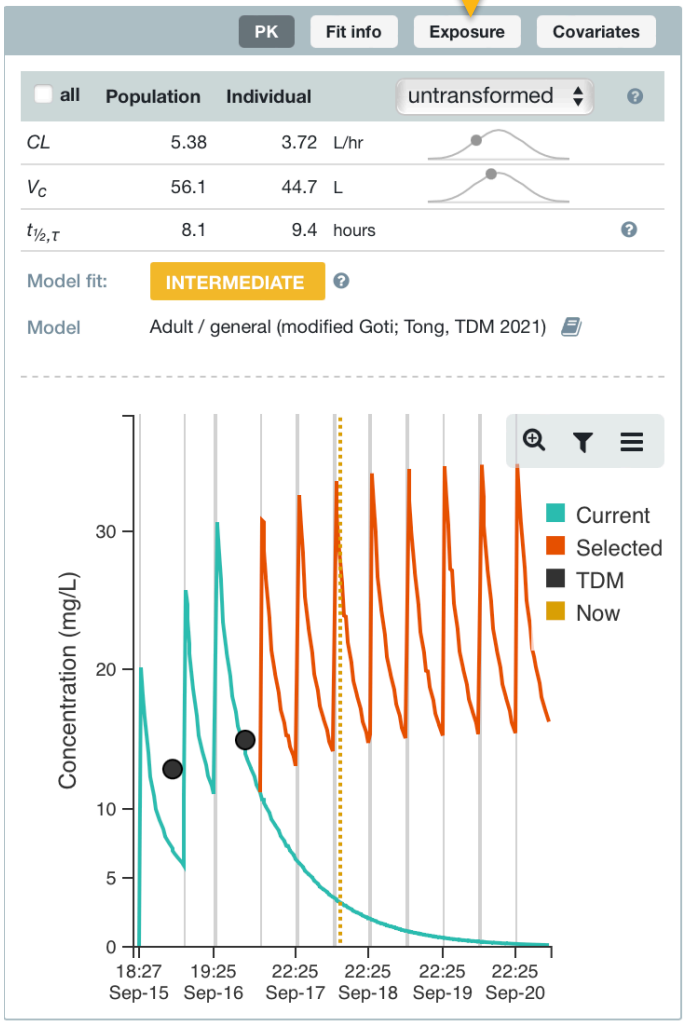
InsightRx: Adjusting a Regimen Based on TDM



Tip: If predicted AUC >500, reduce dose if possible

InsightRx: Adjusting a Regimen Based on TDM

Tip: Check the Exposure tab to see predicted troughs/AUCs on chosen regimen

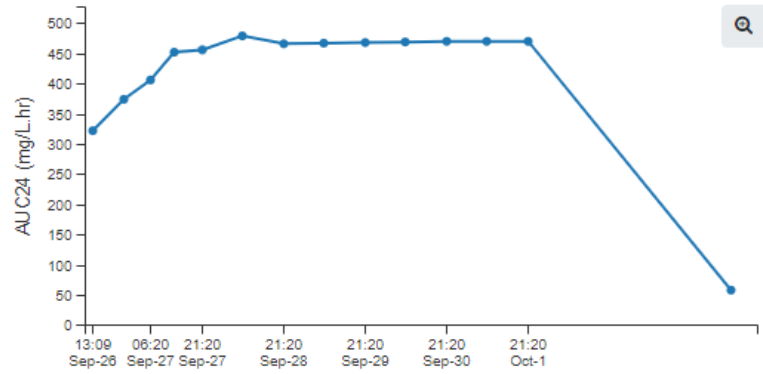


InsightRx: Adjusting a Regimen Based on TDM

PK | Fit info | Exposure | Covariates

Exposure table

	Dose	t_{end}	AUC24	C_{trough}
1	1000 mg	6.633 hours	322 mg/L.hr	7.8 mg/L
2	1000 mg	15.767 hours	374 mg/L.hr	7.4 mg/L
3	1000 mg	23.8 hours	406 mg/L.hr	9.2 mg/L
4	1000 mg	30.8 hours	452 mg/L.hr	11.1 mg/L
5	1000 mg	38.8 hours	456 mg/L.hr	10.4 mg/L
6	1500 mg	50.8 hours	479 mg/L.hr	8.6 mg/L
7	1500 mg	62.8 hours	466 mg/L.hr	8.6 mg/L
8	1500 mg	74.8 hours	467 mg/L.hr	8.6 mg/L
9	1500 mg	86.8 hours	468 mg/L.hr	8.7 mg/L
10	1500 mg	98.8 hours	469 mg/L.hr	8.7 mg/L
11	1500 mg	110.8 hours	470 mg/L.hr	8.7 mg/L
12	1500 mg	122.8 hours	470 mg/L.hr	8.7 mg/L
13	1500 mg	134.8 hours	470 mg/L.hr	8.7 mg/L
		∞	58 mg/L.hr	



Tip: Use this tab to see estimations of future/previous AUCs and to assist with estimating AUC when predicted trough does not match true measured trough

Case Continued

Ortho is consulted and he is taken to the OR. He is found to have significant tendon and tissue necrosis consistent with flexor tenosynovitis and osteomyelitis of the distal phalanx. Patient underwent distal interphalangeal amputation. Intraoperative cultures grow 1+ coagulase-negative staphylococcus and 1+ MRSA. Vancomycin MIC is 1 mg/L. Blood cultures are negative.

The following levels are obtained at steady state while he is on vancomycin 1750 mg every 12 hr, with each infusion given over 2 hr
Last dose of vancomycin given at 0500 and completed at 0700
Peak level 30.4 mg/L at 0900 (2 hours after completion of dose)
Trough level 14.6 mg/L at 1800 (13 hours after dose)
SCr remains stable at 0.9 mg/dL

2. What dose of vancomycin is most appropriate based on these findings?
   a. Continue 1750 mg q12h
   b. 750 mg q8h
   c. 1500 mg q12h
   d. 1250 mg q12h

Case Continued

Patient returns to the OR for repeat wash-out on hospital day 4; due to continued presence of purulent material, revised amputation of the distal interphalangeal is performed. Cultures show MRSA.

SCr increases from 0.9 to 2.0 mg/dL.

3. What is a reasonable approach to therapeutic drug monitoring given the patients AKI?
    a. Continue 1750 mg q12h, SCr increase due to postoperative fluctuation.
    b. Decrease to 1250 mg q12h
    c. Decrease to 750 mg q12h
    d. Hold vancomycin and check random levels 12-24 hours later. Re-dose when concentration is <15 mg/L.

Tip: If you already have a level in InsightRx, you can use InsightRx to guide when you will order the random level and/or help predict when the level will be low enough to resume dosing

Case Continued

Over the next few days, the SCr decreases and stabilizes at 1 mg/dL

Repeat AUC ~518 mg*h/L on vancomycin 1250 mg every 12hr (**trough 12.2 mg/dL**) – patient is at steady state.

Due to presence of continued skin necrosis, patient then undergoes another wash-out and revision amputation at the metacarpophalangeal joint on hospital day 9. Cultures are negative and pathology results are pending at the time of discharge. The ID team is planning a total 4-6 week course

4. Which of the following dosing regimens is most appropriate for this patient at discharge (assuming renal function stays the same)?
    a. Decrease to 1000 mg q12h (predicted trough 9.6, AUC 414)
    b. Continue 1250 mg q12h (predicted trough 12.3, AUC 518)
    c. Change to 2000 mg q24h (predicted trough 5, AUC 415)
    d. Change to 750 mg q8h (predicted trough 13.4, AUC 466)

Tip: Choose the least frequent dosing interval for convenience. Use once daily whenever possible; especially for long courses and OPAT discharges. (Usual cap = 2g daily)

General Tips

Use InsightRx for all patients on vancomycin except those requiring dialysis

- Check daily, especially with any changes in renal function
- **Do the predictions make sense?** Does the patient need another level and/or dose adjustment?

Goal AUC24 is 400-600, but AUC24 in the 500-600 range still may increase risk of AKI

- Usually attempt to keep AUC **400-500**
- Trough doesn't matter—**choose the least frequent dosing regimen for convenience**
- **Avoid q18h and q36h regimens** for simplicity

Utilize all levels drawn

- No need to re-draw trough if drawn at the incorrect time*
- **Reassess model fit with new levels**

If none of the available models fit, double check data entry, consider getting a level at an alternative sampling time (i.e., peak or morning labs), and/or consult ASP

*Possible exception: levels drawn during infusion

Questions & Feedback

Molly Miller, PharmD, BCIDP
molmiller@nebraskamed.com
ASP Pager 888-0349

Nebraska Medicine