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MODEL INFORMED PRECISION DOSING IN PEDIATRIC INTENSIVE CARE UNITS: A RANDOMIZED CLINICAL TRIAL

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Background

Model-informed precision dosing (MIPD) also called Target Concentration Intervention (TCI) is a hybrid machine learning/PK approach to optimizing targeted dose using maximum a posteriori (MAP) Bayesian estimation and population-specific parameters such as PK/PD, age, sex, weight.

Background

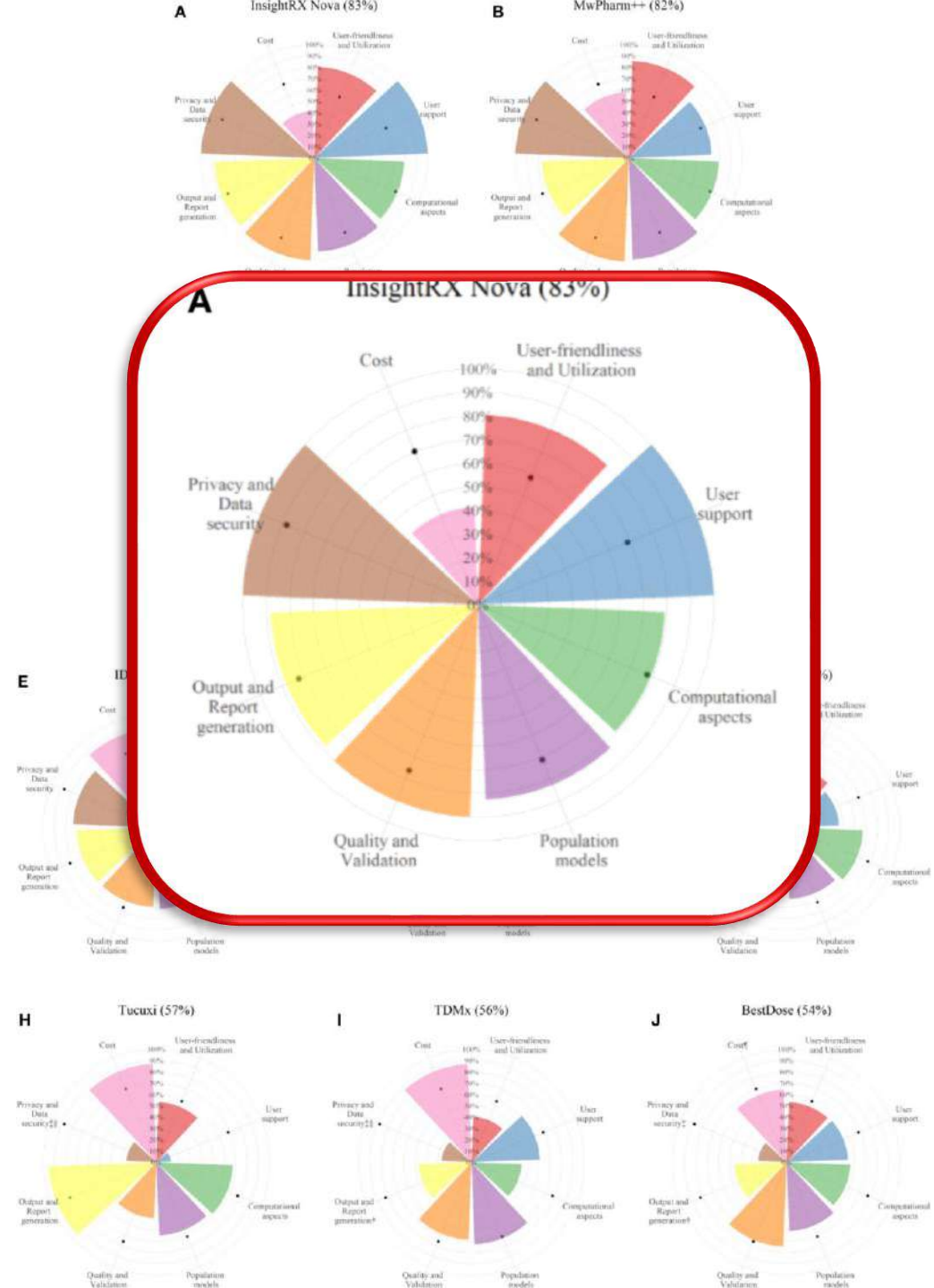
TDM	TCI
TDM has no clear target. It provides a therapeutic window in which the appropriate dose can be included.	TCI has a single target. The target can be easily used to calculate an appropriate dose.
TDM provides a concentration measurement.	TCI uses PK/PD principles to estimate individual parameters so that the appropriate dose can be calculated.
TDM does not provide guidance to the clinician as it is limited to the therapeutic range. Dose adjustments are often experimental rather than based on quantitative pharmacological rationale.	TCI recommends the target dose using individual parameters (e.g. renal clearance). This provides guidance to the clinician.

Aim

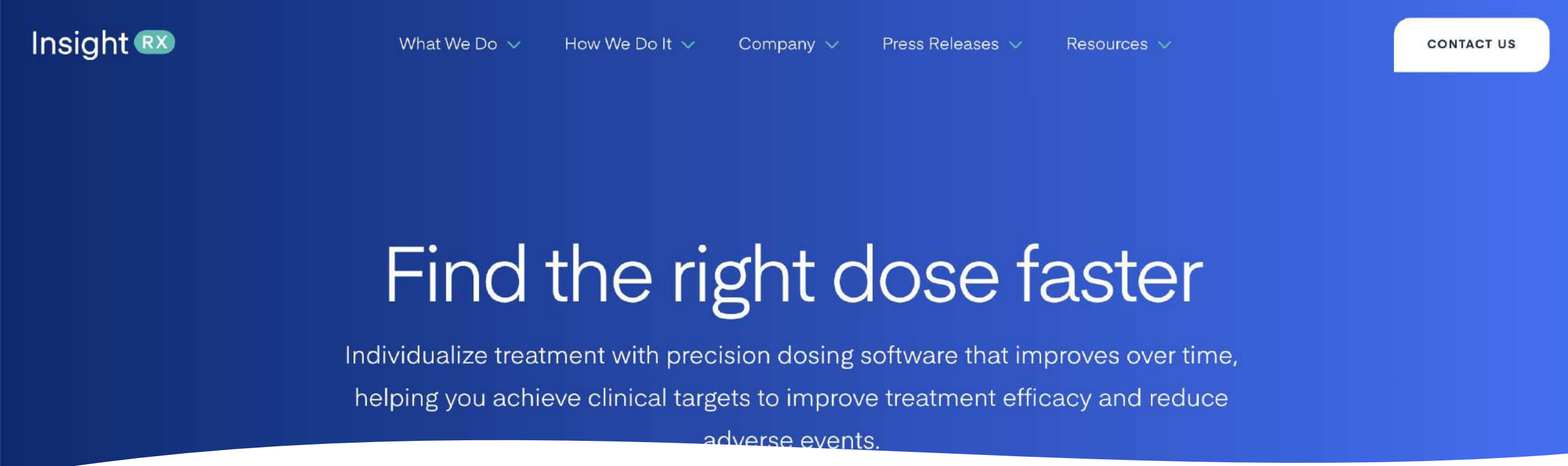
This prospective study aimed to compare to MIPD-based dose adjustments versus standard dosing in terms of the duration of treatment, adverse events and mortality.

Methods

- This pilot study was conducted between January and June 2024 in a Pediatric Intensive Care Unit (PICU).
- The patients were randomly assigned to MIPD (intervention) and standard (control) dosing.
- This study used the MIPD tool named InsightRx® program to compare the difference between predicted and observed plasma levels, including patients treated with amikacin, vancomycin, or fluconazole and had at least one TDM evaluated.



Kantasiripitak W, et al. Software Tools for Model-Informed Precision Dosing: How Well Do They Satisfy the Needs? Front Pharmacol. 2020 May 7;11:620.



Insight RX

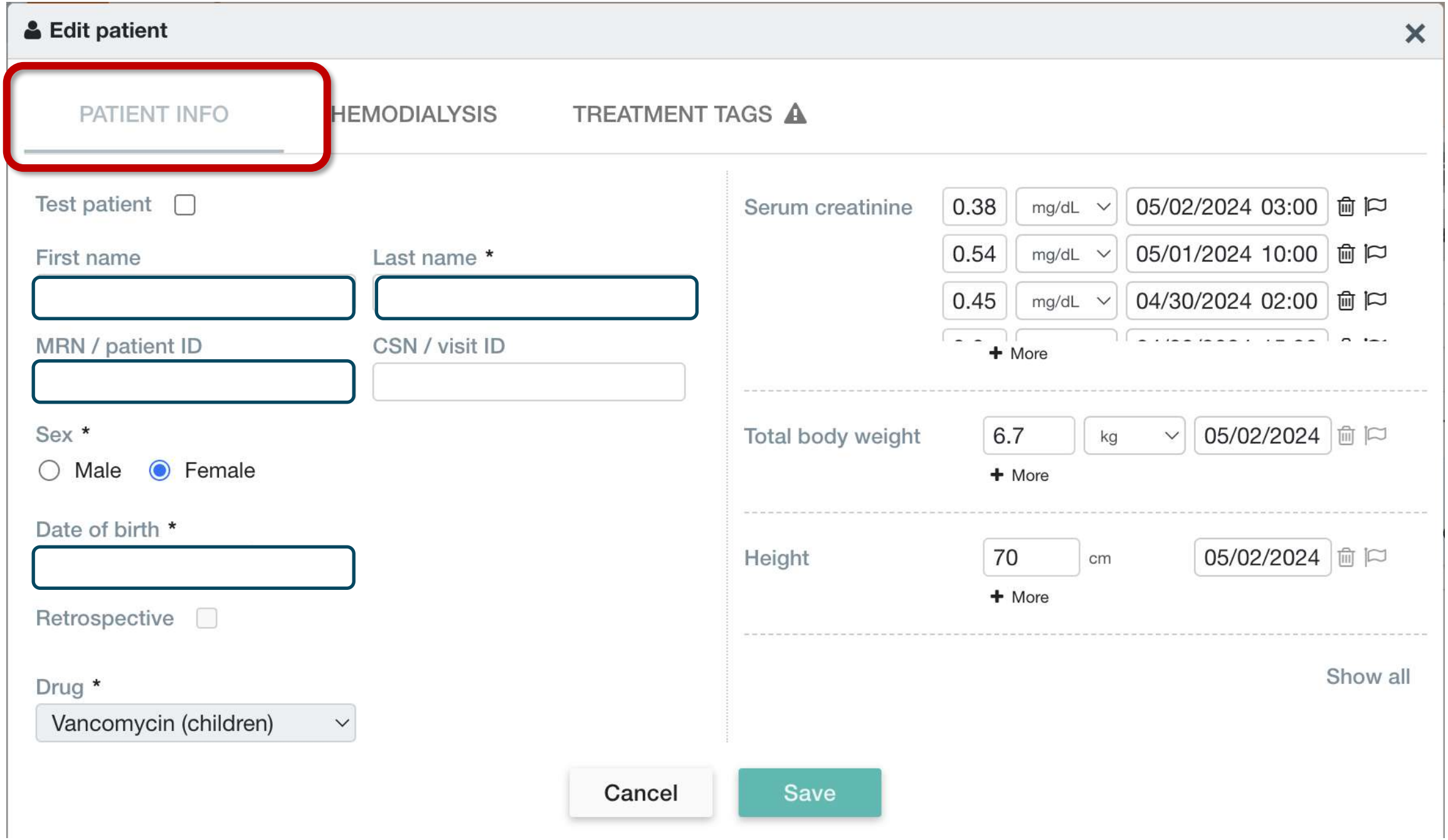
USA (2015)

Web-based: **www.insight-rx.com/**

PopPk and MAP Bayesian forecasting

For adults, pediatrics and newborns

Antibiotics, anticoagulants, antifungals, antineoplastics, antipsychotics, digoxin, immunsupressants, metadon , etc.


Edit patient
PATIENT INFO
HEMODIALYSIS
TREATMENT TAGS
Test patient
First name
Last name *
MRN / patient ID
CSN / visit ID
Sex *
Male
Female
Date of birth *
Retrospective
Drug *
Vancomycin (children)
Serum creatinine
0.38
mg/dL
05/02/2024 03:00
0.54
mg/dL
05/01/2024 10:00
0.45
mg/dL
04/30/2024 02:00
More
Total body weight
6.7
kg
05/02/2024
More
Height
70
cm
05/02/2024
More
Show all
Cancel
Save

Edit patient

PATIENT INFO | HEMODIALYSIS | TREATMENT TAGS

Hemodialysis simulation method:

Manually enter additional drug clearance

Info:

Additional clearance method: For each HD session, please provide the expected *additional clearance* from the hemodialysis. The entered values will be added to the model-predicted drug clearance.

HIDE

No hemodialysis sessions defined for this patient.

+ Add session

Cancel | Save

Edit patient

PATIENT INFO | HEMODIALYSIS | TREATMENT TAGS

Info:
Treatment tags are for data analytics only and do not impact predictions for active treatment courses.

Hospital unit: PICU ×

ICU
NICU
CVICU

Indications

Co-treatment options: ECMO ×

Co-morbidities: Select options

Co-medications: Diuretics × Vasopressors ×

Required*

Cancel Save

Edit patient

PATIENT INFO | HEMODIALYSIS | TREATMENT TAGS

Info:
Treatment tags are for data analytics only and do not impact predictions for active treatment courses.

Hospital unit: PICU ×

Indications: Pneumonia ×

Co-treatment options

Co-morbidities

Co-medications: Diuretics × Vasopressors ×

Required*

- Urinary tract infection (UTI)
- Cellulitis (mild - moderate)
- Cellulitis (severe)

Cancel | Save

Edit patient

PATIENT INFO | HEMODIALYSIS | TREATMENT TAGS ⚠

Info:
Treatment tags are for data analytics only and do not impact predictions for active treatment courses.

Hospital unit: PICU ×

Indications: Pneumonia ×

Co-treatment options: ⚠ ECMO ×

Co-morbidities:
- ⚠ hemodialysis
- ⚠ CRRT

Co-medications: Diuretics × Vasopressors ×

Required*

Cancel | Save

Edit patient

PATIENT INFO | HEMODIALYSIS | TREATMENT TAGS

Info:
Treatment tags are for data analytics only and do not impact predictions for active treatment courses.

Hospital unit: PICU ×

Indications: Pneumonia ×

Co-treatment options: ECMO ×

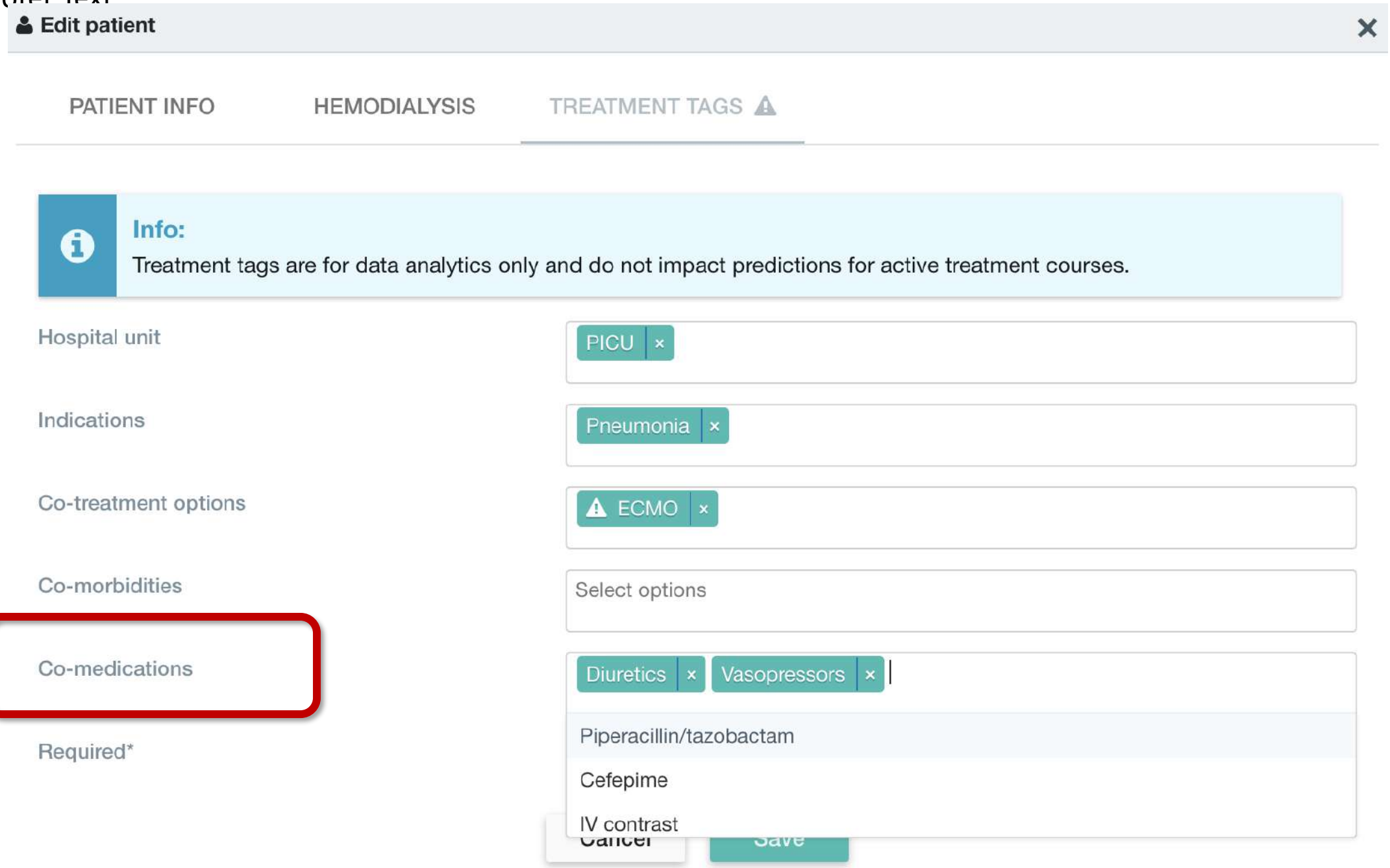
Co-morbidities: Select options

- Oncology / BMT
- Cystic fibrosis

Co-medications

Required*

Cancel | Save


Edit patient
PATIENT INFO
HEMODIALYSIS
TREATMENT TAGS
Info:
Treatment tags are for data analytics only and do not impact predictions for active treatment courses.
Hospital unit
PICU
Indications
Pneumonia
Co-treatment options
ECMO
Co-morbidities
Select options
Co-medications
Diuretics
Vasopressors
Piperacillin/tazobactam
Cefepime
IV contrast
Required*

the study population on which this model was built, so parameters and exposure estimates may be less predictive than expected. Please apply clinical judgement when individualizing dosage.

Date of birth	09/28/2023
Age	7.1 months
Sex	Female

Vancomycin (children)

Notes

Clinical info

Edit

Serum creatinine	0.38 mg/dL	05/02/2024
Total body weight	6.7 kg	05/02/2024
Height	70 cm	05/02/2024
Creatinine assay	Jaffe	
GFR est. method	Schwartz revised	
GFR est. (absolute)	15.4 mL/min	
GFR est. (relative)	76.1 mL/min/1.73m²	
Weight for GFR est.	Total body weight	
Baseline sCr	0.4 mg/dL	
AKI (KDIGO)	No AKI	
BSA	0.35 m²	
BMI	13.7 kg/m2	

Help

Dose information

Update

Target guidance AUC24 (range): 400-600 mg/L.hr

last updated a few seconds ago

steady state concentrations are calculated 4 days out from 05/02/2024

Loading dose

Custom dose

Δ	Dose		Interval	Inf. length	$AUC_{24,ss}$	$C_{trough,ss}$	P_{AUC}*	P_{conc}*
☐		mg	6 hours	1 hours				

Reference table

Δ	Dose	Interval	Inf. length	$AUC_{24,ss}$	$C_{trough,ss}$	P_{AUC}*	P_{conc}*
☐ -30 %	70 mg (10.4 mg/kg)	6 hours	1 hours	341 mg/L.hr	8.4 mg/L	35 %	5 %
☐ -15 %	85 mg (12.7 mg/kg)	6 hours	1 hours	414 mg/L.hr	10.2 mg/L	53 %	11 %
☑ **DoseAssist**	**100 mg (14.9 mg/kg)**	**6 hours**	**1 hours**	**487 mg/L.hr**	**11.9 mg/L**	**68 %**	**18 %**
☐ +15 %	115 mg (17.2 mg/kg)	6 hours	1 hours	559 mg/L.hr	13.7 mg/L	79 %	26 %
☐ +30 %	130 mg (19.4 mg/kg)	6 hours	1 hours	632 mg/L.hr	15.5 mg/L	87 %	34 %

Summary | Generate PDF

* P_{auc}: probability that AUC is >400 (efficacy); P_{conc}: probability that C_{trough} is above 20 µg/mL (toxicity)

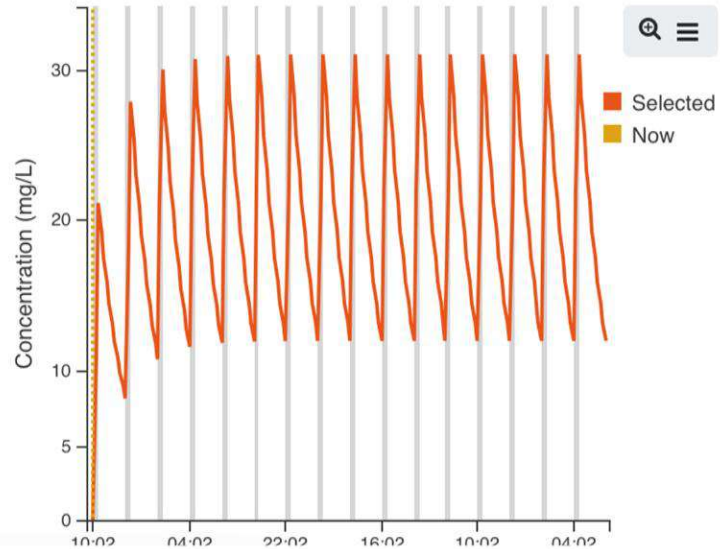
PK | Fit info | Exposure | Covariates

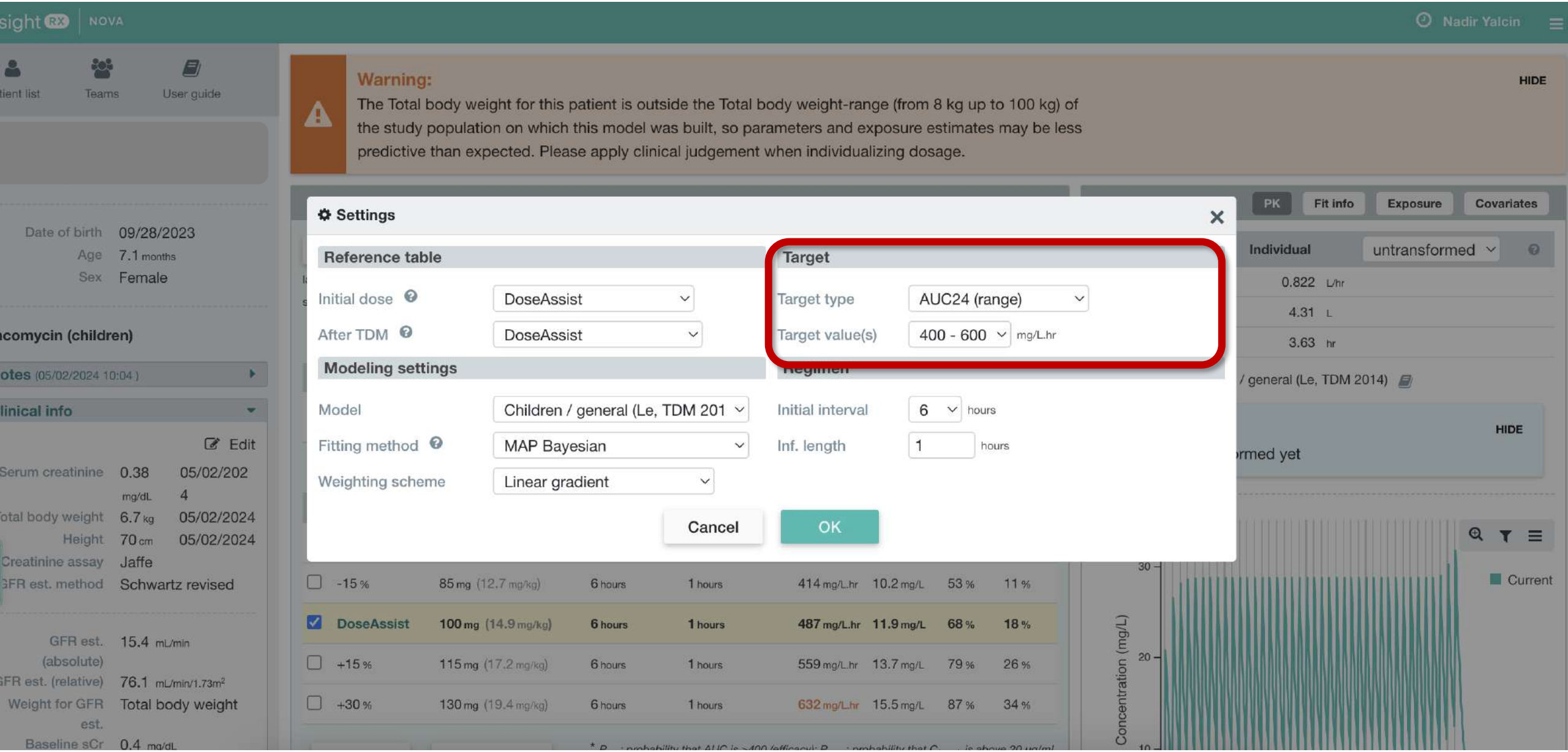
all	Population	Individual	untransformed
CL	0.822	0.822	L/hr
V_c	4.31	4.31	L
$t_{½}$	3.63	3.63	hr

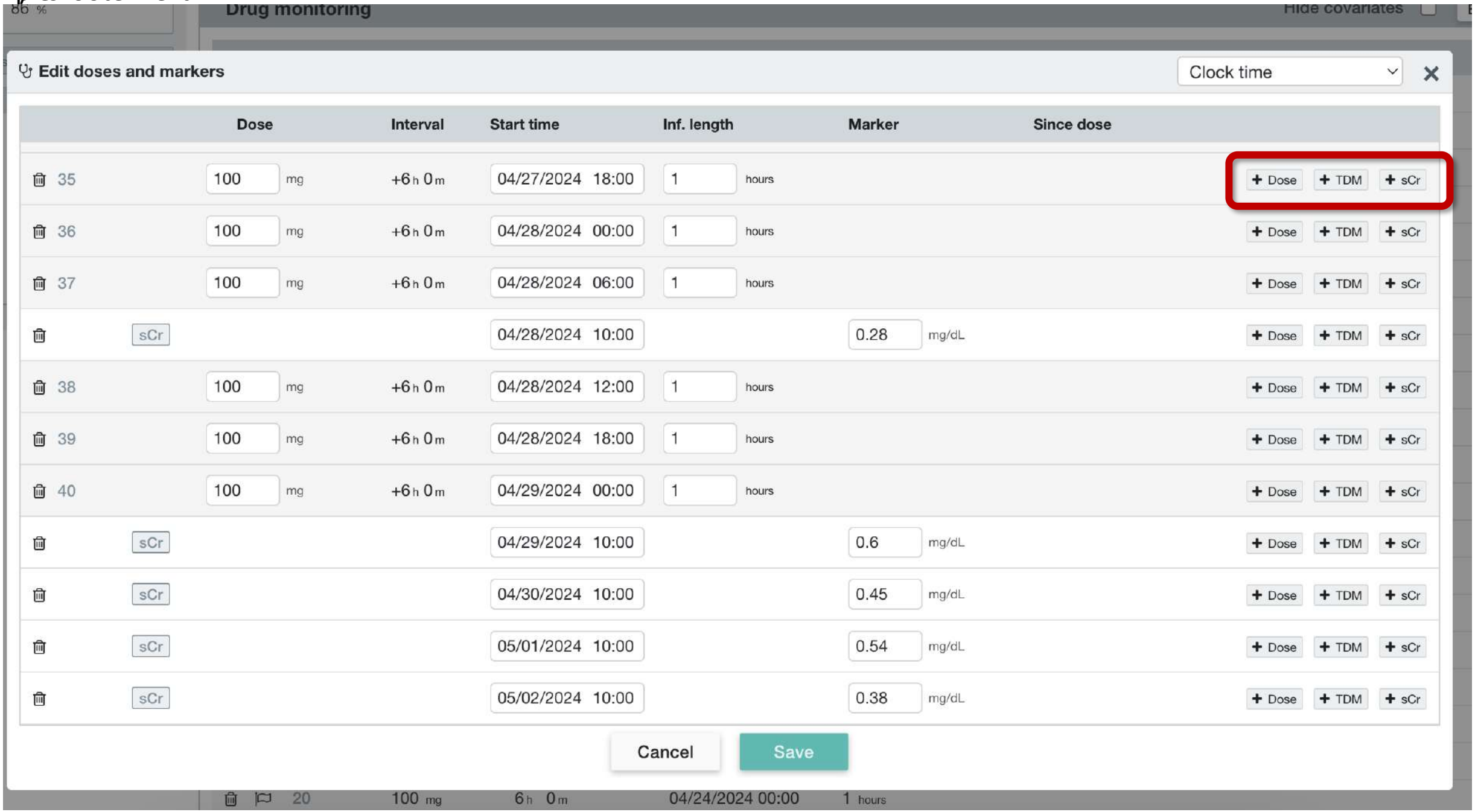
Model: Children / general (Le, TDM 2014)

Info: HIDE

No fit performed yet




sight RX
NOVA
Nadir Yalcin
tient list
Teams
User guide
Warning:
The Total body weight for this patient is outside the Total body weight-range (from 8 kg up to 100 kg) of the study population on which this model was built, so parameters and exposure estimates may be less predictive than expected. Please apply clinical judgement when individualizing dosage.
HIDE
Date of birth 09/28/2023
Age 7.1 months
Sex Female
comycin (children)
otes (05/02/2024 10:04)
linical info
Edit
Serum creatinine 0.38 mg/dL 05/02/202 4
Total body weight 6.7 kg 05/02/2024
Height 70 cm 05/02/2024
Creatinine assay Jaffe
GFR est. method Schwartz revised
GFR est. (absolute) 15.4 mL/min
GFR est. (relative) 76.1 mL/min/1.73m²
Weight for GFR est. Total body weight
Baseline sCr 0.4 mg/dL
Settings
Reference table
Initial dose DoseAssist
After TDM DoseAssist
Modeling settings
Model Children / general (Le, TDM 201
Fitting method MAP Bayesian
Weighting scheme Linear gradient
Target
Target type AUC24 (range)
Target value(s) 400 - 600 mg/L.hr
Regimen
Initial interval 6 hours
Inf. length 1 hours
Cancel
OK
-15 % 85 mg (12.7 mg/kg) 6 hours 1 hours 414 mg/L.hr 10.2 mg/L 53 % 11 %
DoseAssist 100 mg (14.9 mg/kg) 6 hours 1 hours 487 mg/L.hr 11.9 mg/L 68 % 18 %
+15 % 115 mg (17.2 mg/kg) 6 hours 1 hours 559 mg/L.hr 13.7 mg/L 79 % 26 %
+30 % 130 mg (19.4 mg/kg) 6 hours 1 hours 632 mg/L.hr 15.5 mg/L 87 % 34 %
PK
Fit info
Exposure
Covariates
Individual untransformed
0.822 L/hr
4.31 L
3.63 hr
/ general (Le, TDM 2014)
HIDE
rmed yet
Current
Concentration (mg/L)
30
20
10


Drug monitoring
Hide covariates
Edit doses and markers
Clock time
Dose
Interval
Start time
Inf. length
Marker
Since dose
35 100 mg +6 h 0 m 04/27/2024 18:00 1 hours + Dose + TDM + sCr
36 100 mg +6 h 0 m 04/28/2024 00:00 1 hours + Dose + TDM + sCr
37 100 mg +6 h 0 m 04/28/2024 06:00 1 hours + Dose + TDM + sCr
sCr 04/28/2024 10:00 0.28 mg/dL + Dose + TDM + sCr
38 100 mg +6 h 0 m 04/28/2024 12:00 1 hours + Dose + TDM + sCr
39 100 mg +6 h 0 m 04/28/2024 18:00 1 hours + Dose + TDM + sCr
40 100 mg +6 h 0 m 04/29/2024 00:00 1 hours + Dose + TDM + sCr
sCr 04/29/2024 10:00 0.6 mg/dL + Dose + TDM + sCr
sCr 04/30/2024 10:00 0.45 mg/dL + Dose + TDM + sCr
sCr 05/01/2024 10:00 0.54 mg/dL + Dose + TDM + sCr
sCr 05/02/2024 10:00 0.38 mg/dL + Dose + TDM + sCr
Cancel
Save
20 100 mg 6 h 0 m 04/24/2024 00:00 1 hours

Insight RX | NOVA

Nadir Yalcin

Patient list | Teams | User guide

Date of birth 09/28/2023
Age 7.1 months
Sex Female

Vancomycin (children)

Notes (05/02/2024 10:04)

Clinical info

Edit

Serum creatinine	0.38 mg/dL	05/02/2024
Total body weight	6.7 kg	05/02/2024
Height	70 cm	05/02/2024
Creatinine assay	Jaffe	
GFR est. method	Schwartz revised	
GFR est. (absolute)	15.4 mL/min	
GFR est. (relative)	76.1 mL/min/1.73m²	
Weight for GFR est.	Total body weight	
Baseline sCr	0.4 mg/dL	

Help

Warning:
The Total body weight for this patient is outside the Total body weight-range (from 8 kg up to 100 kg) of the study population on which this model was built, so parameters and exposure estimates may be less predictive than expected. Please apply clinical judgement when individualizing dosage.

HIDE

Dose information

Update | Target guidance AUC24 (range): 400-600 mg/L.hr

last updated a few seconds ago

steady state concentrations are calculated 4 days out from 05/02/2024

Custom dose

Δ	Dose		Interval	Inf. length	$AUC_{24,ss}$	$C_{trough,ss}$	P_{AUC}*	P_{conc}*
☐		mg	6 hours	1 hours				

Reference table

Δ	Dose	Interval	Inf. length	$AUC_{24,ss}$	$C_{trough,ss}$	P_{AUC}*	P_{conc}*
☐ -30 %	70 mg (10.4 mg/kg)	6 hours	1 hours	341 mg/L.hr	8.4 mg/L	35 %	5 %
☐ -15 %	85 mg (12.7 mg/kg)	6 hours	1 hours	414 mg/L.hr	10.2 mg/L	53 %	11 %
☑ **DoseAssist**	**100 mg (14.9 mg/kg)**	**6 hours**	**1 hours**	**487 mg/L.hr**	**11.9 mg/L**	**68 %**	**18 %**
☐ +15 %	115 mg (17.2 mg/kg)	6 hours	1 hours	559 mg/L.hr	13.7 mg/L	79 %	26 %
☐ +30 %	130 mg (19.4 mg/kg)	6 hours	1 hours	632 mg/L.hr	15.5 mg/L	87 %	34 %

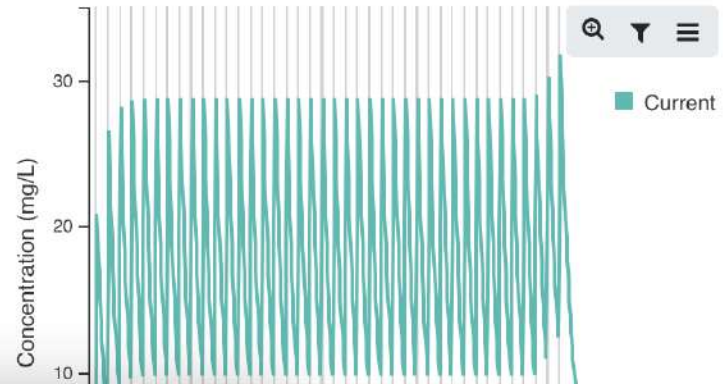
* P_{auc}: probability that AUC is >400 (efficacy); P_{conc}: probability that C_{trough} is above 20 µg/mL

PK | Fit info | Exposure | Covariates

☑ all	Population	Individual	untransformed
CL	0.822	0.822 L/hr	
V_c	4.31	4.31 L	
$t_{½}$	3.63	3.63 hr	

Model: Children / general (Le, TDM 2014)

Info: HIDE
No fit performed yet



Dose information

Update

Target guidance AUC24 (range): 400-600 mg/L.hr

st updated a few seconds ago, starting with dose #59 at 05/03/2024 18:00

eady state concentrations are calculated 4 days out from 05/03/2024

Custom dose

Δ	Dose	Interval	Inf. length	$AUC_{24,ss}$	$C_{trough,ss}$	P_{AUC}*	P_{conc}*
☐	mg	6 hours	1 hours				

Reference table

Δ	Dose	Interval	Inf. length	$AUC_{24,ss}$	$C_{trough,ss}$	P_{AUC}*	P_{conc}*
☐ -30 %	70 mg (10.4 mg/kg)	6 hours	1 hours	352 mg/L.hr	8.8 mg/L	14 %	0 %
☐ -15 %	85 mg (12.7 mg/kg)	6 hours	1 hours	428 mg/L.hr	10.7 mg/L	71 %	0 %
☑ **DoseAssist**	**100 mg (14.9 mg/kg)**	**6 hours**	**1 hours**	**503 mg/L.hr**	**12.6 mg/L**	**97 %**	**0 %**
☐ +15 %	115 mg (17.2 mg/kg)	6 hours	1 hours	579 mg/L.hr	14.5 mg/L	100 %	3 %
☐ +30 %	130 mg (19.4 mg/kg)	6 hours	1 hours	654 mg/L.hr	16.4 mg/L	100 %	12 %

Summary Generate PDF

* *P_{auc}: probability that AUC is >400 (efficacy); P_{conc}: probability that C_{trough} is above 20 µg/mL (toxicity)*

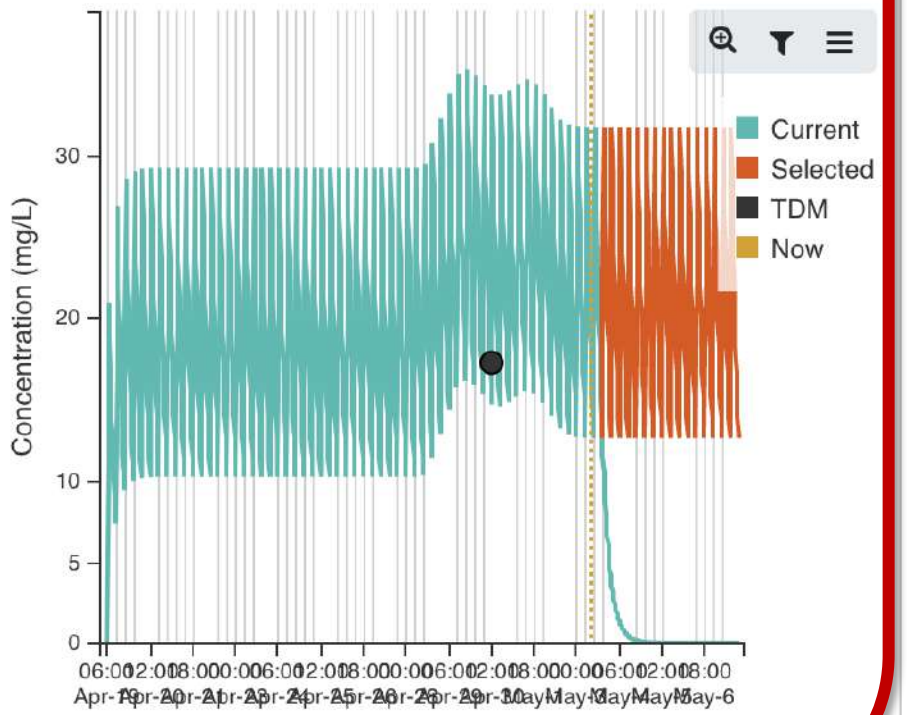
Simulate doses 16 doses starting later at 05/03/2024 18:00 Add doses

PK | Fit info | Exposure | Covariates

all	Population	Individual	untransformed
CL	0.814	0.795 L/hr	
V_c	4.31	4.32 L	
$t_{½}$	3.67	3.77 hr	

Model fit: GOOD

Model: Children / general (Le, TDM 2014)



the study population on which this model was built, so parameters and exposure estimates may be less predictive than expected. Please apply clinical judgement when individualizing dosage.

Dose information

Update | **Target guidance** AUC24 (range): 400-600 mg/L.hr

last updated a few seconds ago, starting with dose #59 at 05/03/2024 18:00

steady state concentrations are calculated 4 days out from 05/03/2024

Custom dose

Δ	Dose	Interval	Inf. length	$AUC_{24,ss}$	$C_{trough,ss}$	P_{AUC}*	P_{conc}*
☐	mg	6 hours	1 hours				

Reference table

Δ	Dose	Interval	Inf. length	$AUC_{24,ss}$	$C_{trough,ss}$	P_{AUC}*	P_{conc}*
☐ -30 %	70 mg (10.4 mg/kg)	6 hours	1 hours	352 mg/L.hr	8.8 mg/L	14 %	0 %
☐ -15 %	85 mg (12.7 mg/kg)	6 hours	1 hours	428 mg/L.hr	10.7 mg/L	71 %	0 %
☑ **DoseAssist**	**100 mg (14.9 mg/kg)**	**6 hours**	**1 hours**	**503 mg/L.hr**	**12.6 mg/L**	**97 %**	**0 %**
☐ +15 %	115 mg (17.2 mg/kg)	6 hours	1 hours	579 mg/L.hr	14.5 mg/L	100 %	3 %
☐ +30 %	130 mg (19.4 mg/kg)	6 hours	1 hours	654 mg/L.hr	16.4 mg/L	100 %	12 %

Summary | Generate PDF

* *P_{auc}: probability that AUC is >400 (efficacy); P_{conc}: probability that C_{trough} is above 20 µg/mL (toxicity)*

Simulate doses 16 doses starting later at 05/03/2024 18:00 Add doses

PK | Fit info | Exposure | Covariates

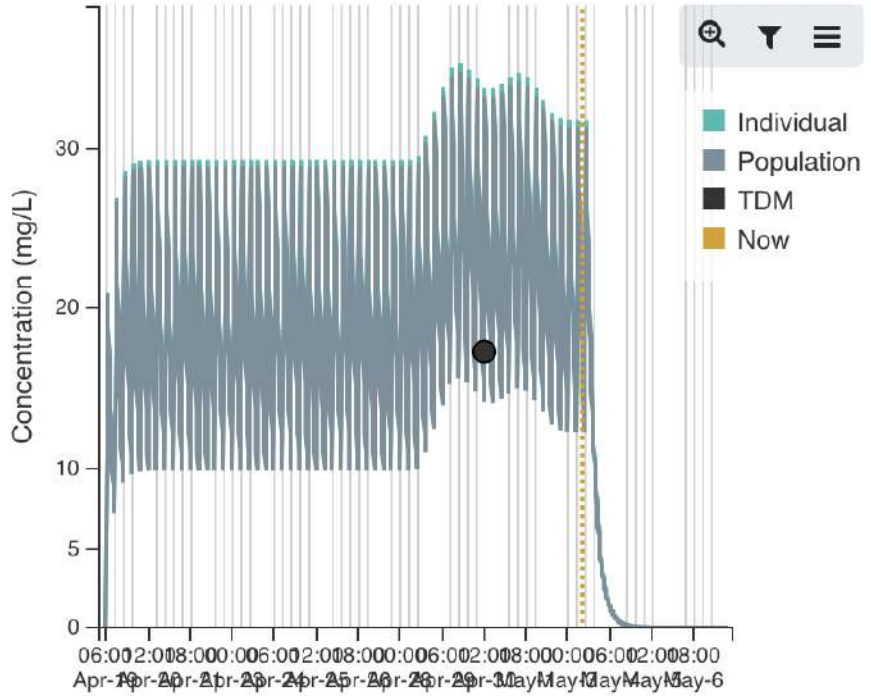
Time	TDM	Prediction	Weight	Fit
04/30/2024 11:30	**17.2**	15.92 mg/L	100%	✓

Model fit: GOOD

Model: Children / general (Le, TDM 2014)

Fitting method: MAP Bayesian

Weighting scheme: Linear gradient



ICON	FIT	SUMMARY	MANAGEMENT
	Good	"reasonable"	no further explanation needed
	Intermediate	"caution"	look for explanations
	Poor	"suspicious"	check data; caution with predictions

Dose information

Update

Target guidance AUC24 (range): 400-600 mg/L.hr

last updated a few seconds ago, starting with dose #59 at 05/03/2024 18:00

steady state concentrations are calculated 4 days out from 05/03/2024

Custom dose

Δ	Dose	Interval	Inf. length	$AUC_{24,ss}$	$C_{trough,ss}$	P_{AUC}*	P_{conc}*
☑	200 mg	6 hours	1 hours	1006 mg/L.hr	25.2 mg/L	100 %	89 %

Reference table

Δ	Dose	Interval	Inf. length	$AUC_{24,ss}$	$C_{trough,ss}$	P_{AUC}*	P_{conc}*
-30 %	70 mg (10.4 mg/kg)	6 hours	1 hours	352 mg/L.hr	8.8 mg/L	14 %	0 %
-15 %	85 mg (12.7 mg/kg)	6 hours	1 hours	428 mg/L.hr	10.7 mg/L	71 %	0 %
DoseAssist	100 mg (14.9 mg/kg)	6 hours	1 hours	503 mg/L.hr	12.6 mg/L	97 %	0 %
+15 %	115 mg (17.2 mg/kg)	6 hours	1 hours	579 mg/L.hr	14.5 mg/L	100 %	3 %
+30 %	130 mg (19.4 mg/kg)	6 hours	1 hours	654 mg/L.hr	16.4 mg/L	100 %	12 %

Summary Generate PDF

* *P_{auc}: probability that AUC is >400 (efficacy); P_{conc}: probability that C_{trough} is above 20 µg/mL (toxicity)*

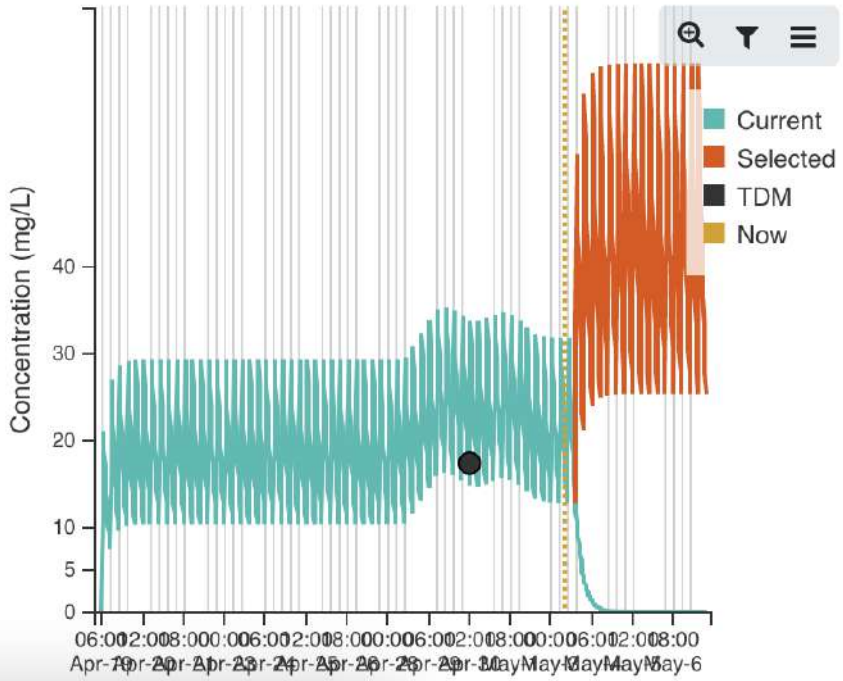
Simulate doses … doses starting … at … Add doses

PK | Fit info | Exposure | Covariates

all	Population	Individual	untransformed
CL	0.814	0.795 L/hr	
V_c	4.31	4.32 L	
$t_{½}$	3.67	3.77 hr	

Model fit: GOOD

Model: Children / general (Le, TDM 2014)



Results

- InsightRx uses population-based modeling to predict patients' TDM scores and categorizes them as “poor”, “intermediate” or “good” to assess the patient's fit to the model.
- Total of 66 patients were admitted to the PICU with relevant treatment, but only 27 (40.9%) met inclusion criteria with 39 TDM [55.6% males, median age 100 months (range:7-548 months)].
- The majority of patients were receiving vancomycin (44.4%), while those receiving amikacin (18.5%) and combination therapy (37.2%) were noted separately.

Results

Distribution of related pharmacotherapy

Medications (N=27)	n	%
Vancomycin	12	44.4
Amikacin	5	18.5
Vancomycin + Amikacin	6	22.4
Amikacin + Fluconazole	2	7.4
Vancomycin + Amikacin + Fluconazole	2	7.4

Results

- Modeling program predicted that 82.1% of 39 TDM levels would be classified as "good." Total of 7 (17.9%) TDMs were subjected to a second assessment, with program correctly identifying 100% of these as within the acceptable level.
- Based on 39 TDM, only 12 (30.8%) recommendations were accepted, with 27 TDM continuing with the existing dose.

Results

- Of the 12 accepted recommendations, 9 were for dose increase and 3 were for dose reduction.
- Among the accepted dose recommendations, 7 of them showed the TDM level for the second time and 2 of them were modified and classified as "good» (the first TDM's were poor and intermediate).
- There were no significant differences between groups in terms of LOS, duration of treatment adverse events and mortality due to small sample size.

Home > Intensive Care Medicine > Article

Model-informed precision dosing of beta-lactam antibiotics and ciprofloxacin in critically ill patients: a multicentre randomised clinical trial

Original | Open access | Published: 09 November 2022
Volume 48, pages 1760–1771, (2022) Cite this article

Download PDF

Intensive Care Medicine

Aims and scope →

Submit manuscript →

Purpose: Individualising drug dosing using model-informed precision dosing (MIPD) of beta-lactam antibiotics and ciprofloxacin has been proposed as an alternative to standard dosing to optimise antibiotic efficacy in critically ill patients. However, randomised clinical trials (RCT) on clinical outcomes have been lacking.

Methods: This multicentre RCT, including patients admitted to the intensive care unit (ICU) who were treated with antibiotics, was conducted in eight hospitals in the Netherlands. Patients were randomised to MIPD with dose and interval adjustments based on monitoring serum drug levels (therapeutic drug monitoring) combined with pharmacometric modelling of beta-lactam antibiotics and ciprofloxacin. The primary outcome was ICU length of stay (LOS). Secondary outcomes were ICU mortality, hospital mortality, 28-day mortality, 6-month mortality, delta sequential organ failure assessment (SOFA) score, adverse events and target attainment.

Results: In total, 388 (MIPD $n = 189$; standard dosing $n = 199$) patients were analysed (median age 64 [IQR 55–71]). We found no significant differences in ICU LOS between MIPD compared to standard dosing (10 MIPD vs 8 standard dosing; IRR = 1.16; 95% CI 0.96–1.41; $p = 0.13$). There was no significant difference in target attainment before intervention at day 1 (T1) (55.6% MIPD vs 60.9% standard dosing; $p = 0.24$) or at day 3 (T3) (59.5% vs 60.4%; $p = 0.84$). There were no significant differences in other secondary outcomes.

Conclusions: We could not show a beneficial effect of MIPD of beta-lactam antibiotics and ciprofloxacin on ICU LOS in critically ill patients. Our data highlight the need to identify other approaches to dose optimisation.

Keywords: Precision dosing, Beta-lactam antibiotics, Ciprofloxacin, Model-informed, Critically ill

Limitations

- Of the 12 accepted recommendations, 9 were for dose increase and 3 were for dose reduction.
- Different population and different covariates
- Antibiotic and antifungal plasma level measure 1 day (Thursday) every week in our hospital.
- Workload and time effort
- Without integration of EHR
- An unorthodox approach for clinicians

Conclusion

- To the best of our knowledge, this is the first RCT about comparison of MIPD vs. standard dosing in PICU for antimicrobials.
- As the sample size and frequency of TDM increase, the feedforward and predictive power of the models will also increase.
- Therefore, there is a need to evaluate different populations in different countries, hospitals and PICUs in terms of covariates such as genetics, age groups and dosage guidelines.

THANK YOU FOR LISTENING

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