Bridging the Gap from Vancomycin Trough to AUC Monitoring

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Conflicts of Interest

- Neither the speakers nor the planning staff have any relevant conflicts of interest to disclose.

Learning Objectives

1. Assess the benefit of precision dosing software as a best practice for vancomycin AUC monitoring.
2. Design a plan to implement precision dosing software in a healthcare system.
3. Predict the challenges of implementing precision dosing software for a variety of hospital types, including those with limited resources.

Hospital Sisters Health System (HSHS)

- HSHS hospitals are located in Illinois (9) and Wisconsin (6)
- Franciscan Catholic Healthcare Ministry
- Mix of critical access, community teaching, and tertiary care hospitals
- System antimicrobial stewardship and pharmacy & therapeutics committees
- 13 of the 15 hospitals on the same EMR platform and clinical decision support

https://line.17qq.com/articles/suesrqcrqx.html.
https://www.sj-r.com/story/news/2021/03/30/hospital-sisters-st-francis-run-spiritual-retreat-closing/7058544002/

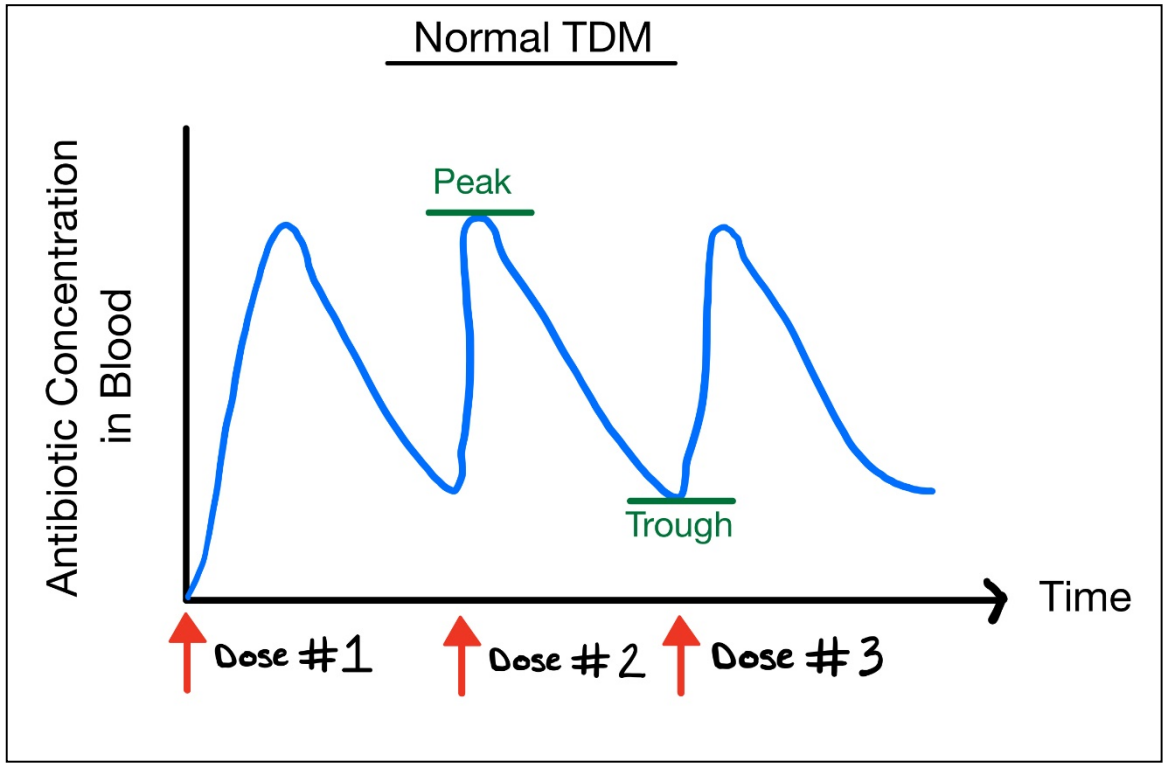
Benefits of AUC-Based Vancomycin Monitoring

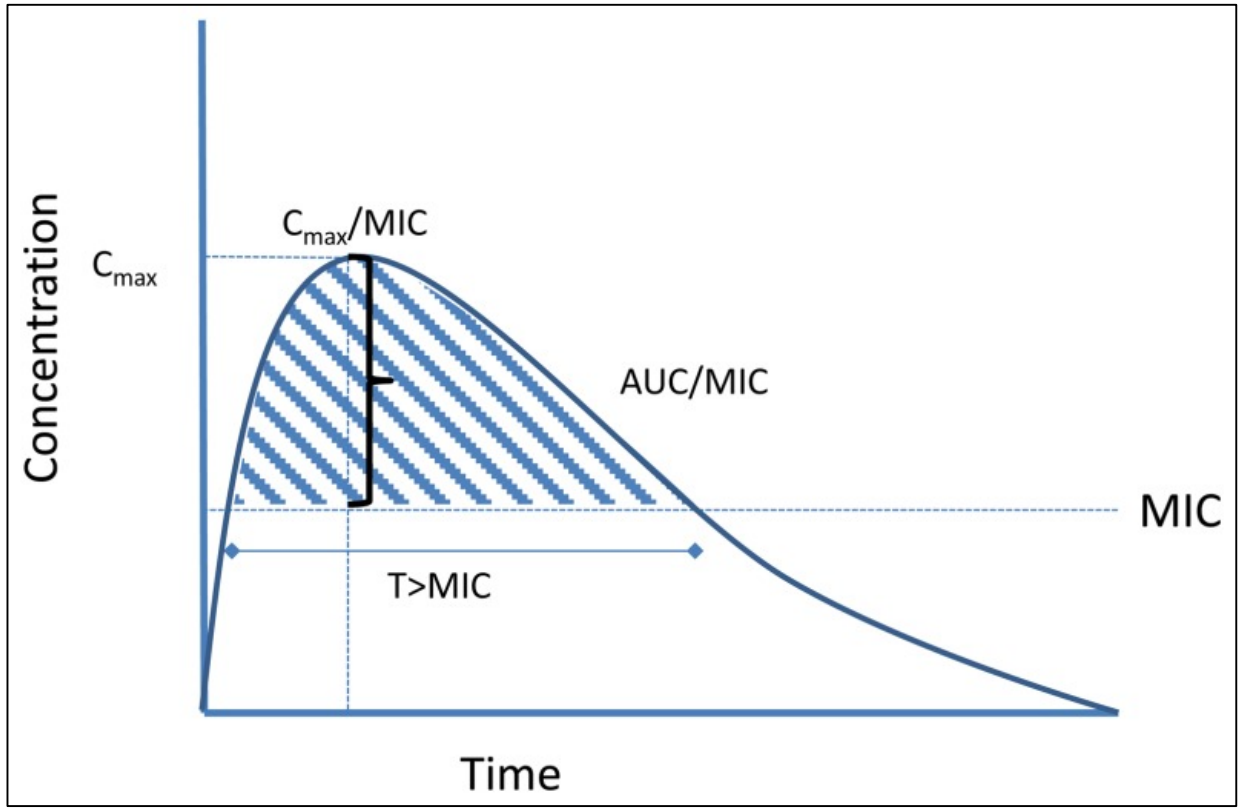
Integrative Activity – Use Handout

Why Implement Vancomycin AUC Monitoring?

- AUC monitoring by a pharmacist provides safer and more effective vancomycin therapy for patients, while decreasing vancomycin and lab utilization for a cost-benefit to healthcare facilities.

Trough vs. AUC





http://www.microbiologynutsandbolts.co.uk/theraputic-drug-monitoring.html
https://www.ncbi.nlm.nih.gov/books/NBK266259/figure/introduction.f1/

Clinical Background

What are the clinical benefits of transitioning from trough to AUC?

Efficacy

Safety

Efficacy Data

- In a simulation of 5000 patients on vancomycin 1g q8h, trough was poorly correlated with AUC
- High inter-patient variability with correlating trough to AUC

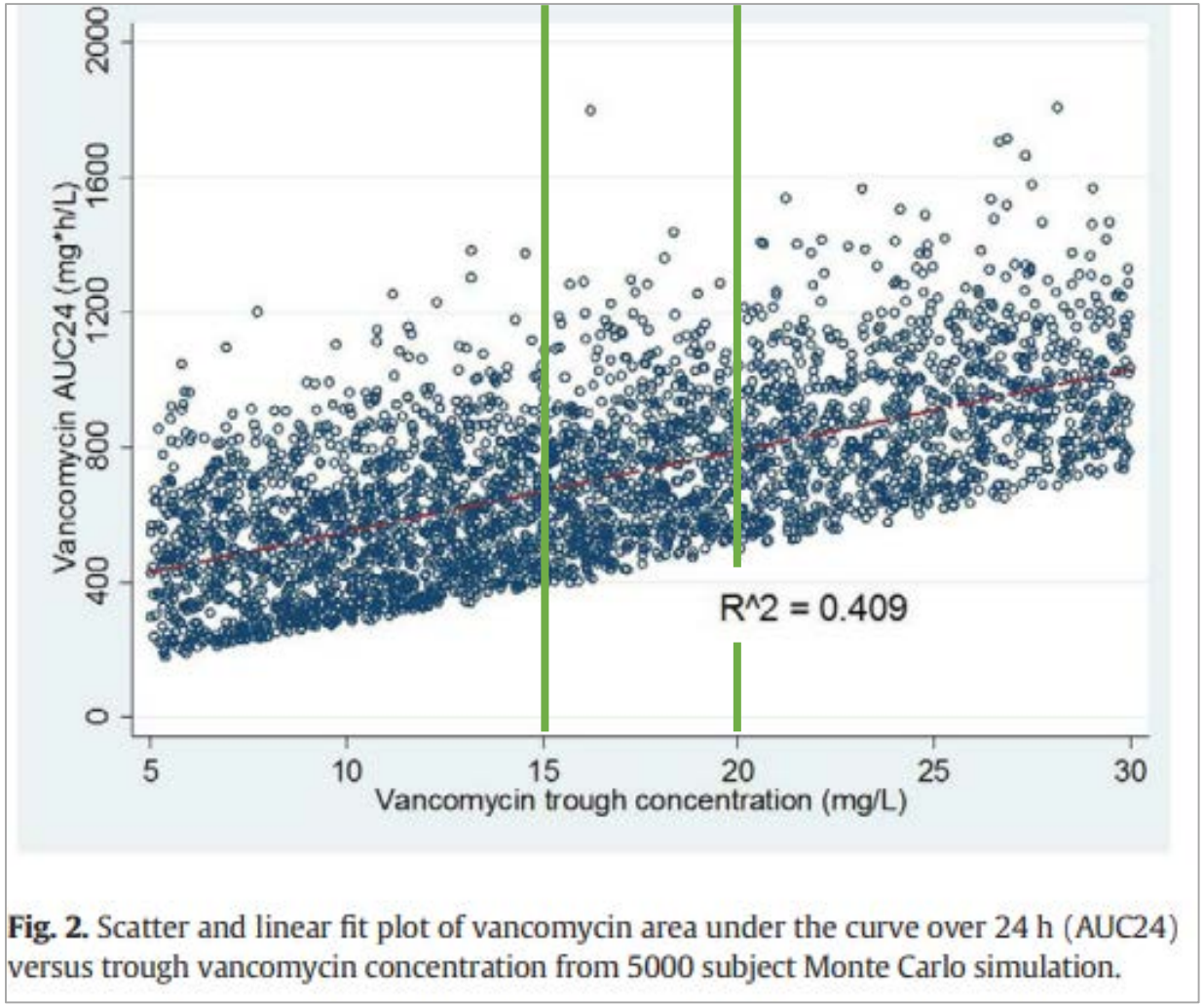
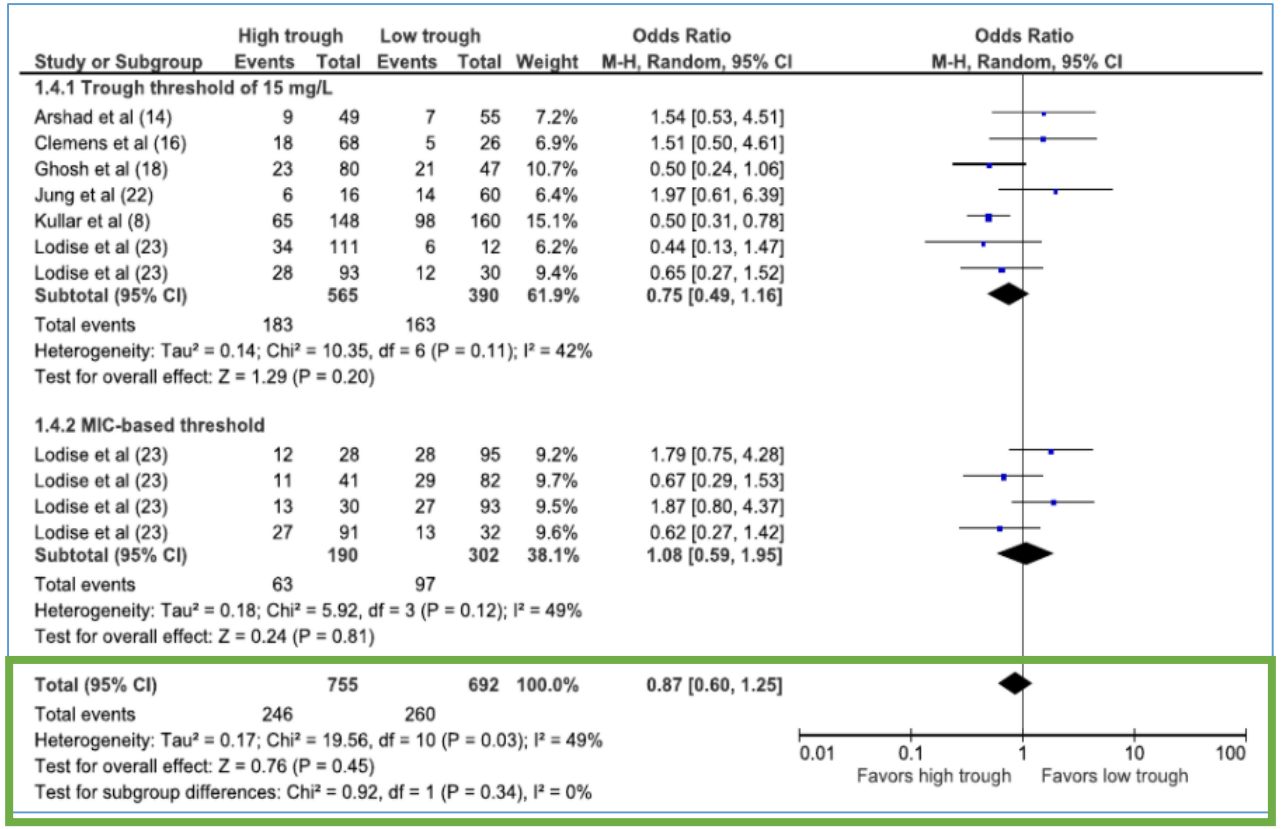


Fig. 2. Scatter and linear fit plot of vancomycin area under the curve over 24 h (AUC24) versus trough vancomycin concentration from 5000 subject Monte Carlo simulation.

Pai MP et al. Advan Drug Deliv Review. 2014;77:50-57.

Efficacy Data

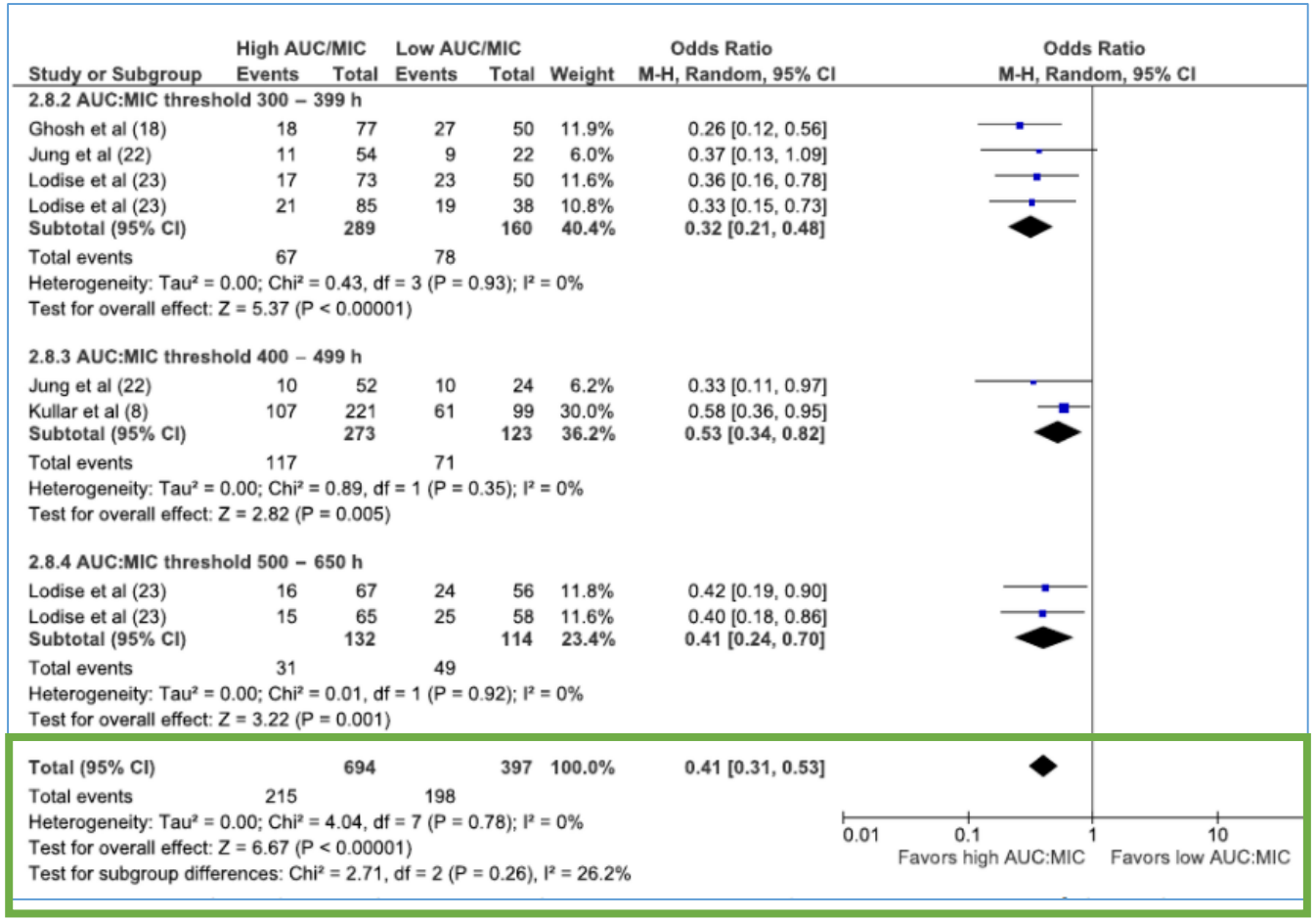
- Meta-analysis looking at association between vancomycin trough level and treatment outcomes
- Treatment failure = mortality or persistent bacteremia
- No difference in vancomycin treatment failure with high (≥ 15 mg/L) vs. low trough



Prybylski JP. Pharmacotherapy. 2015;35(19):889-898.

Efficacy Data

- Meta-analysis looking at association between vancomycin trough level and treatment outcomes
- Association between AUC:MIC and vancomycin treatment failure
- High AUC (≥ 400) associated with reduction in treatment failure



Prybylski JP. Pharmacotherapy. 2015;35(19):889-898.

Nephrotoxicity Data

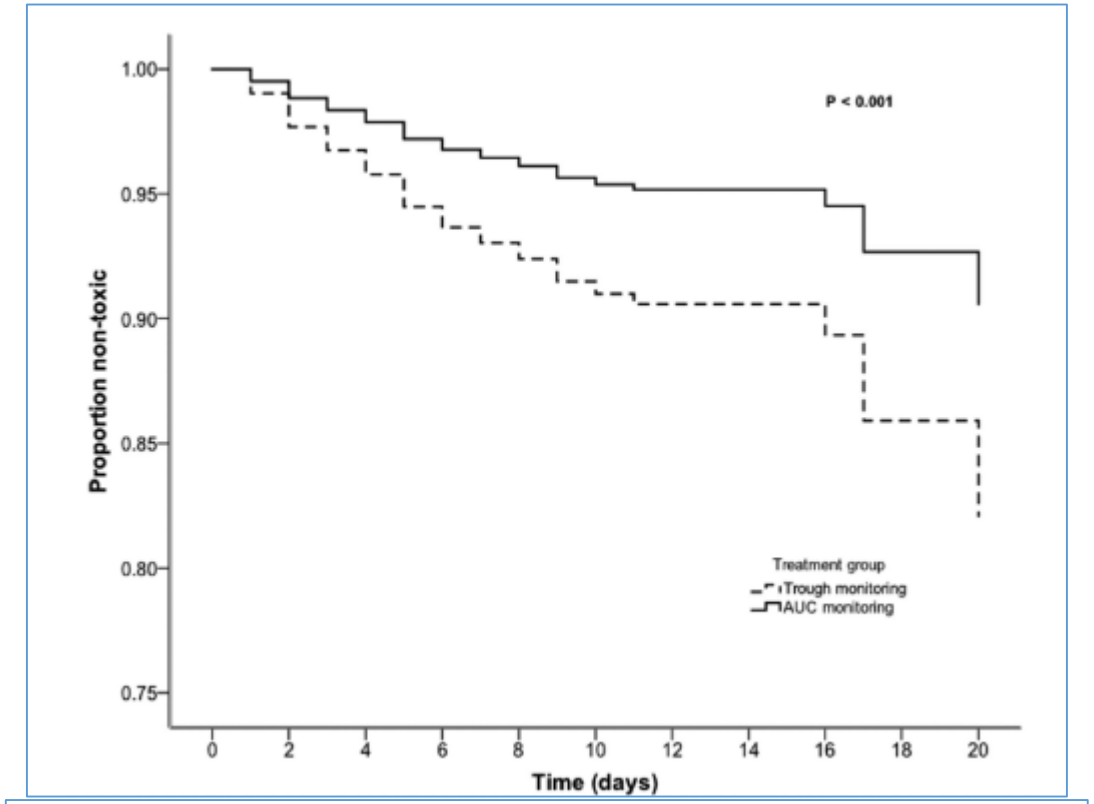


FIG 1 Time to nephrotoxicity by Cox proportional hazards regression. AUC-TD, AUC- and trough concentration-guided dosing.

- Quasi-experimental study of 1280 patients
- AUC monitoring demonstrated reduction in nephrotoxicity as well as decreased time to nephrotoxicity

Finch NA et al. Antimicrob Agents Chemother. 2017;61(2).

Nephrotoxicity Data

- Multivariable logistic regression found AUC monitoring associated with ~ 50% reduction in nephrotoxicity

TABLE 2 Multivariable logistic regression for 2009 vancomycin consensus guideline-defined nephrotoxicity

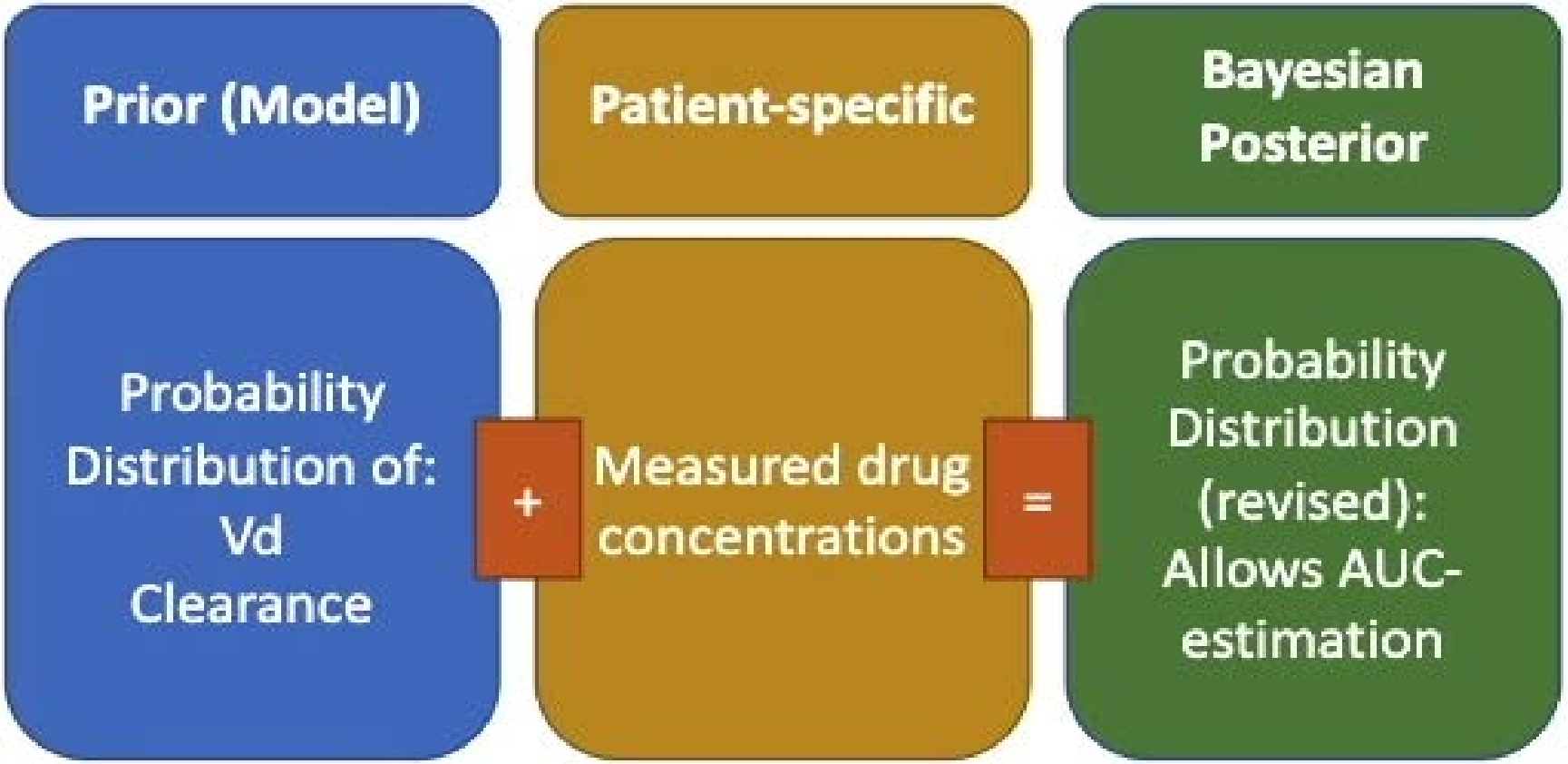
Variable	Unadjusted OR	95% CI for unadjusted OR	Adjusted OR	95% CI for adjusted OR	*P* value
AUC monitoring	0.724	0.488–1.074	0.514	0.332–0.794	0.003
Concomitant furosemide	3.226	2.136–4.873	1.771	1.127–2.784	0.013
Elixhauser comorbidity index	1.274	1.186–1.368	1.149	1.060–1.245	0.001
Duration of therapy	1.124	1.074–1.175	1.093	1.044–1.145	<0.001
APACHE II score	1.084	1.061–1.106	1.070	1.045–1.097	<0.001
Concomitant i.v. contrast dye	2.406	1.538–3.765			
Concomitant tobramycin	1.195	0.880–4.165			

Finch NA et al. Antimicrob Agents Chemother. 2017;61(2).

How Do I Calculate AUC?

- Two methods for calculating AUC
  - Two-sample AUC calculations by hand or using spreadsheet
    - Pros: Inexpensive technology, quick setup and implementation
    - Cons: More lab draws, levels must be at steady-state, more room for human error, time-consuming
  - One-sample AUC calculations using Bayesian software
    - Pros: Fewer lab draws, less room for human error, more efficient
    - Cons: Increased costs for technology, longer setup and implementation, downtime

Bayesian Method



Pai MP et al. Advan Drug Deliv Review. 2014;77:50-57.
Rybak MJ. Implementing the 2020 Vancomycin Guidelines [webinar]. Accessed September 8, 2020.

Cost-Benefit

- Lee BV, et al. published a detailed cost analysis comparing 3 groups: trough-only, non-Bayesian AUC monitoring, and Bayesian AUC monitoring
- Trough group – Standard of care set by 2009 IDSA guidelines
- Non-Bayesian: Two-sample AUC monitoring using spreadsheet
- Bayesian: One-sample monitoring using precision dosing software
- Drug levels completed within first 48 hours of treatment
- Outcomes monitored from 48 hours to end of therapy

Lee, BV et al. Cost-benefit analysis comparing trough, two-level AUC and Bayesian AUC dosing for vancomycin. *Clin Micro Infect.* 19 November 2020. https://doi.org/10.1016/j.cmi.2020.11.008

Cost-Benefit

Specific costs that were included:

- Vancomycin drug concentrations
- Bayesian software costs
- Hospitalizations for Acute Kidney Injury (AKI)

Cost-Benefit

Dosing Method	Trough (US $)	Two-sample AUC (US $)	Bayesian AUC (US $)
Additional AKI treatment cost per patient	2,982	2,136	917
Incremental Cost Benefit per Patient vs Trough	-	846	2065
Incremental Cost Benefit for 1000 Vancomycin Patients/Year vs Trough	-	846,810	2,065,720

Lee, BV et al. Cost-benefit analysis comparing trough, two-level AUC and Bayesian AUC dosing for vancomycin. *Clin Micro Infect.* 19 November 2020. https://doi.org/10.1016/j.cmi.2020.11.008

Cost-Benefit

Other potential cost and time savings:

- Decreased drug costs
- Decreased nursing and laboratory time for lab draws
- Increased pharmacist productivity due to time efficiency

Lee, BV et al. Cost-benefit analysis comparing trough, two-level AUC and Bayesian AUC dosing for vancomycin. *Clin Micro Infect.* 19 November 2020. https://doi.org/10.1016/j.cmi.2020.11.008

Integrative Activity – Use Handout

Crunch the Numbers!

- Cost avoidance:
- 2,065,720 dollars/year per 1000 vancomycin patients

= $2,065.72 saved per patient!

Integrative Activity – Use Handout

Break-even analysis for Bayesian Precision Dosing Software

- Cost of Software:
- $100,000 annual cost/$2,065.72 cost avoidance per patient

= 41 vancomycin patients per year

Implementation

"You do not rise to the level of your goals.

You fall to the level of your systems."

- James Clear, "Atomic Habits"

Make a Detailed To-Do List

Integrative Activity – Use Handout

How do I get started?

1. Find your experts and build your team

Key Players

- Infectious Diseases Pharmacist
- Infectious Diseases Physician
- Director of Pharmacy / Pharmacy Manager
- Pharmacy Informatics
- Financial Analyst
- Hospital Leadership

Hospital / System Committees

- Antimicrobial Stewardship
- Pharmacy & Therapeutics
- Fiscal Stewardship
- Informatics

Integrative Activity – Use Handout

Leadership Buy-In

1. Present clinical data and break-even analysis for your specific institution or institutions.
2. Assess whether implementation makes sense on a local or system level.
3. Decide which Bayesian precision dosing software platform is the best fit.
    - Turner RB. Pharmacotherapy. 2018;38(12):1174-1183.

Integrative Activity – Use Handout

Build Your Systems

- Calculation decisions
- Bayesian Software Data Validation
- Vancomycin Monitoring Protocol
- Work-aids
- Educational Materials
  - Pharmacists
  - Nurses
  - Physicians/Mid-level providers

Integrative Activity – Use Handout

Education & Training

Pharmacists

- Clinical Education – continuing education programs, IDSA guidelines
- Software Training – live classes, videos, practice
- Proof of Competency – CE certificates, competencies, patient case studies
- Question/Answer sessions

Integrative Activity – Use Handout

Education & Training

<u>Physicians, Mid-level Providers, Nurses</u>

- Memos
- Committee meetings
- Department huddles
- Email
- Onboarding

Integrative Activity – Use Handout

After Go-Live

- Troubleshooting
- Evaluation – revise protocol, patient case studies, communication of common errors

Excellent Implementation Resources

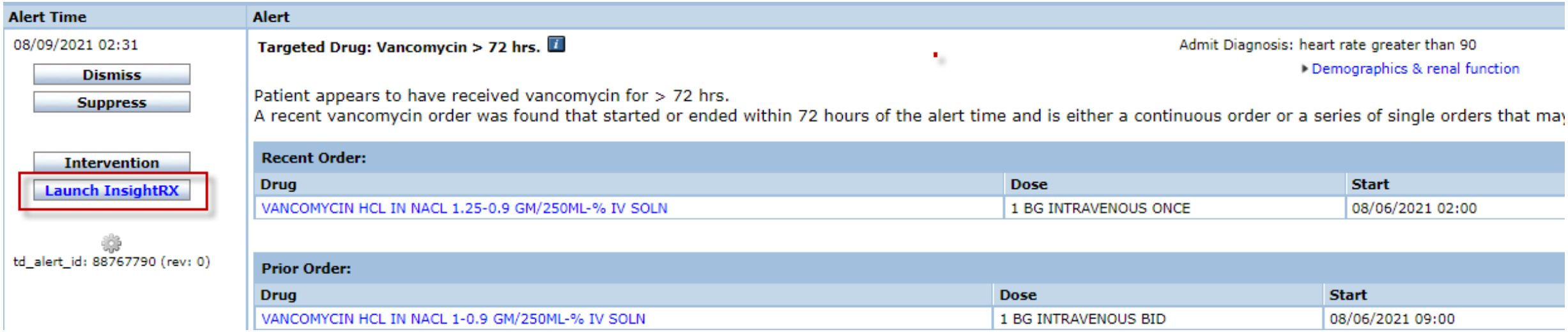
- https://mad-id.org/vancomycin/
- https://www.sidp.org/Vancomycin-AUC-Implementation-Toolkit-Guide
- https://www.proce.com/activities/activity_detail?id=869
- Heil EL, Claeys KC, Mynatt RP, et al. Making the change to area under the curve-based vancomycin dosing. *Am J Health-Syst Pharm*. 2018;75:1986-1995.

Workflow Considerations

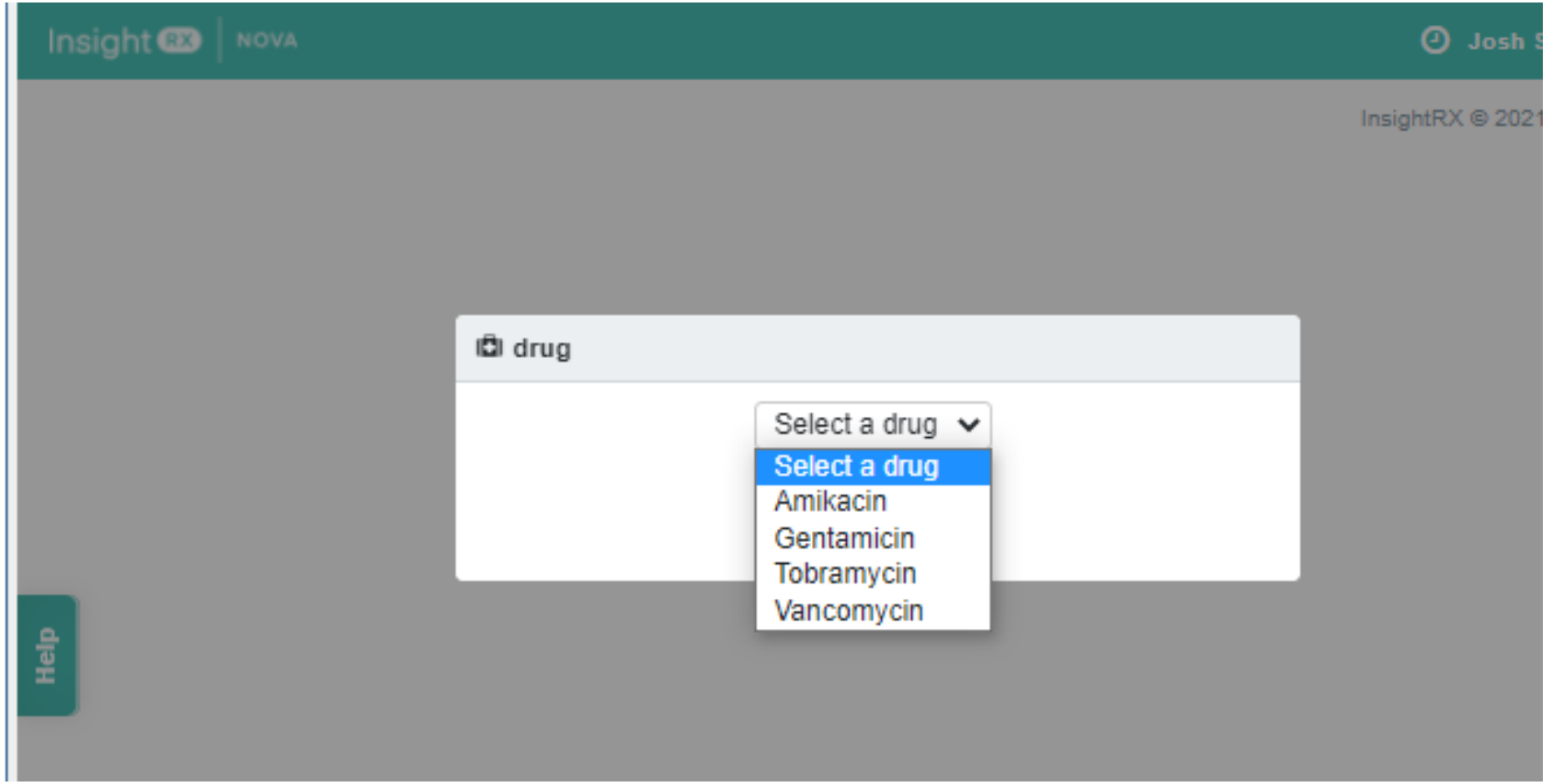
Workflow Overview

- Pick your patient
- Pick your medication
- Review data
- Perform analysis
- Copy decision into progress note

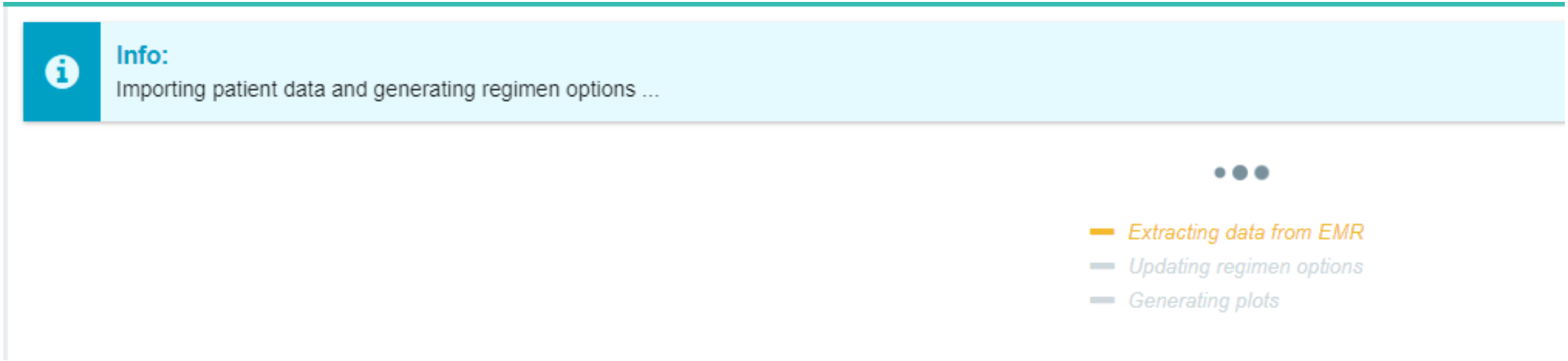
Launch Tool


Alert Time
Alert
08/09/2021 02:31
Dismiss
Suppress
Intervention
Launch InsightRX
td_alert_id: 88767790 (rev: 0)
Targeted Drug: Vancomycin > 72 hrs.
Admit Diagnosis: heart rate greater than 90
Demographics & renal function
Patient appears to have received vancomycin for > 72 hrs.
A recent vancomycin order was found that started or ended within 72 hours of the alert time and is either a continuous order or a series of single orders that may
Recent Order:
Drug
Dose
Start
VANCOMYCIN HCL IN NACL 1.25-0.9 GM/250ML-% IV SOLN
1 BG INTRAVENOUS ONCE
08/06/2021 02:00
Prior Order:
Drug
Dose
Start
VANCOMYCIN HCL IN NACL 1-0.9 GM/250ML-% IV SOLN
1 BG INTRAVENOUS BID
08/06/2021 09:00

Select Drug

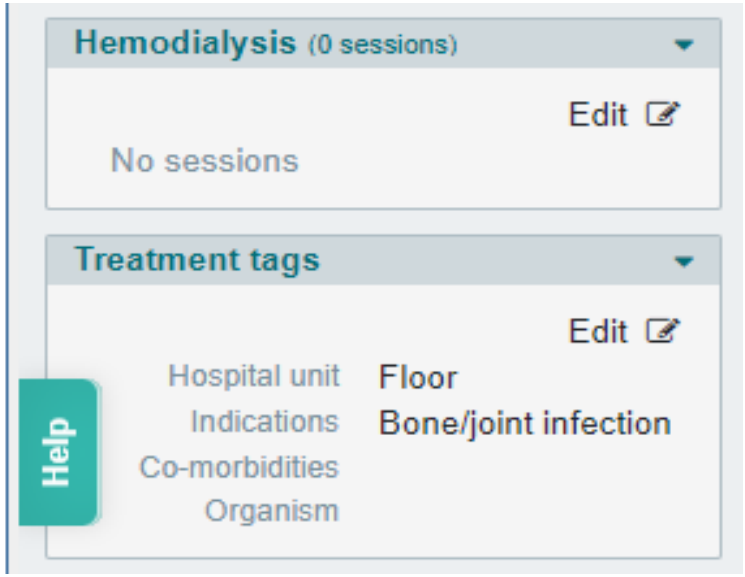

Insight RX
NOVA
Josh S
InsightRX © 2021
drug
Select a drug
Select a drug
Amikacin
Gentamicin
Tobramycin
Vancomycin
Help

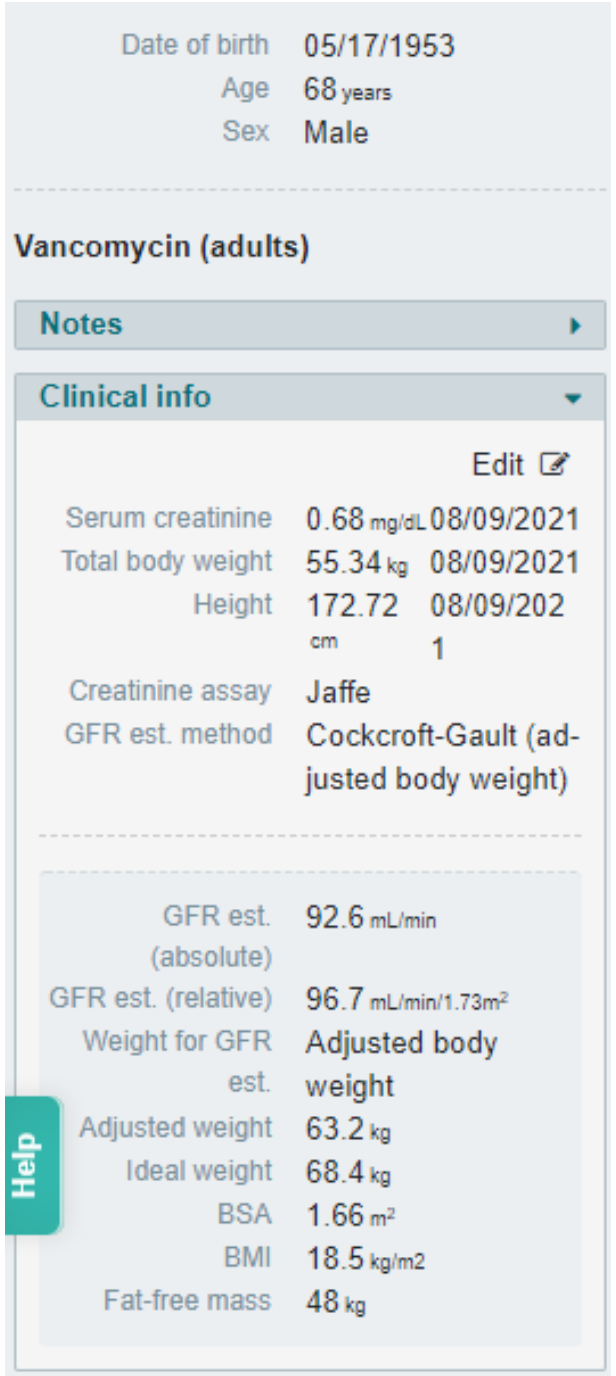
Data Extraction



Review Pertinent Data

- Interfaced lab data and calculations
- Non-interfaced data (e.g. hemodialysis)





Historical Timing

- Past doses, levels, labs
- Calculated interval, infusion length

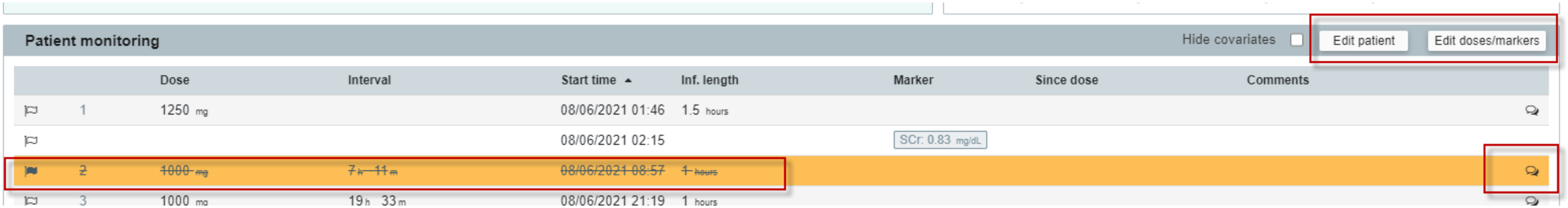
Patient monitoring

Hide covariates ☐ | Edit patient | Edit doses/markers

		Dose	Interval	Start time ▲	Inf. length	Marker	Since dose	Comments
⚐	1	1250 mg		08/06/2021 01:46	1.5 hours			
⚐				08/06/2021 02:15		SCr: 0.83 mg/dL		
⚐	2	1000 mg	7 h 11 m	08/06/2021 08:57	1 hours			
⚐	3	1000 mg	12 h 22 m	08/06/2021 21:19	1 hours			
⚐	4	1000 mg	11 h 25 m	08/07/2021 08:44	1 hours			
⚐	5	1000 mg	13 h 29 m	08/07/2021 22:13	1 hours			
⚐				08/08/2021 06:57		TDM: 16.1 MCG/ML	8 h 44 m	
⚐	6	1000 mg	12 h 39 m	08/08/2021 10:52	1 hours			
⚐	7	1000 mg	10 h 45 m	08/08/2021 21:37	1 hours			
⚐	8	1000 mg	10 h 51 m	08/09/2021 08:28	1 hours			
⚐				08/09/2021 10:21		SCr: 0.68 mg/dL		

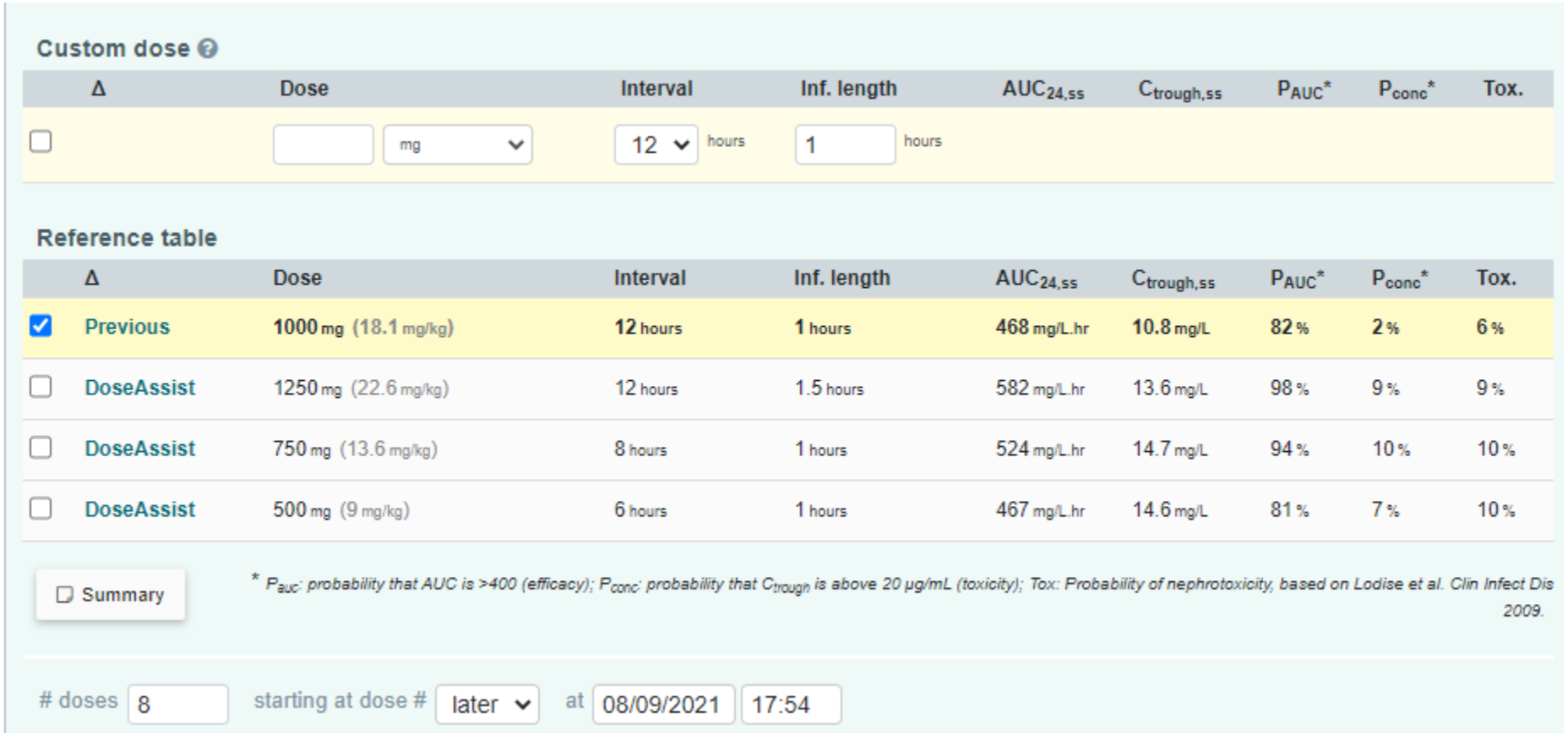
Timing Interactions

- Flag or remove data inaccuracies
- Tag comments to data
- Edit to add missing troughs or doses
  - How do you handle an outage with an integrated solution?



Dose Analysis

- Review guidance on different dosing regimens



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.
☑ Previous	1000 mg (18.1 mg/kg)	12 hours	1 hours	468 mg/L.hr	10.8 mg/L	82 %	2 %	6 %
☐ DoseAssist	1250 mg (22.6 mg/kg)	12 hours	1.5 hours	582 mg/L.hr	13.6 mg/L	98 %	9 %	9 %
☐ DoseAssist	750 mg (13.6 mg/kg)	8 hours	1 hours	524 mg/L.hr	14.7 mg/L	94 %	10 %	10 %
☐ DoseAssist	500 mg (9 mg/kg)	6 hours	1 hours	467 mg/L.hr	14.6 mg/L	81 %	7 %	10 %

☐ Summary

* *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.*

doses 8 starting at dose # later at 08/09/2021 17:54

Select New Dose

- Alter dosing to see the impact over time

Reference table

	Δ	Dose	Interval	Inf. length	$AUC_{24,ss}$	$C_{trough,ss}$	P_{AUC}*	P_{conc}*	Tox.
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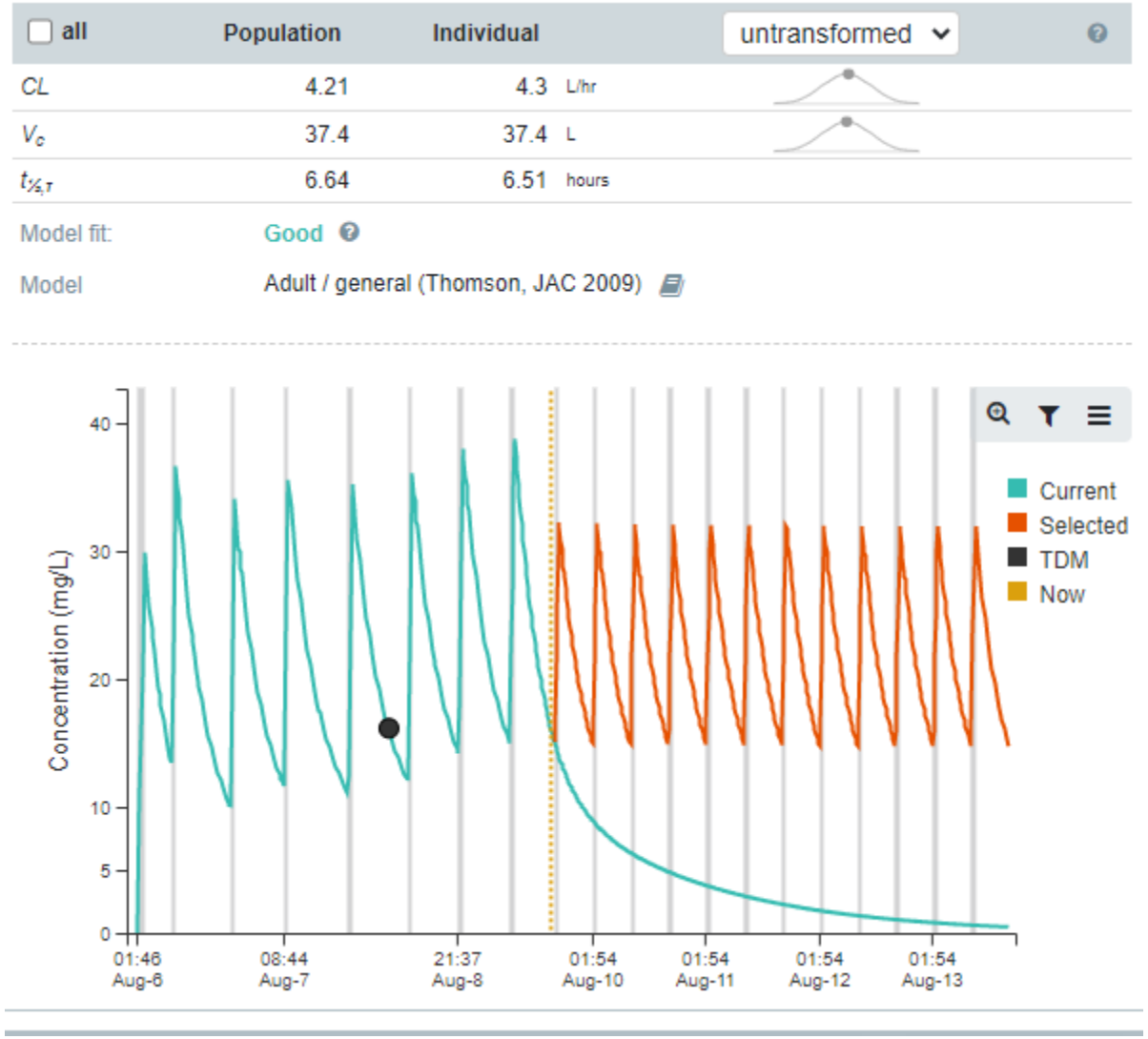
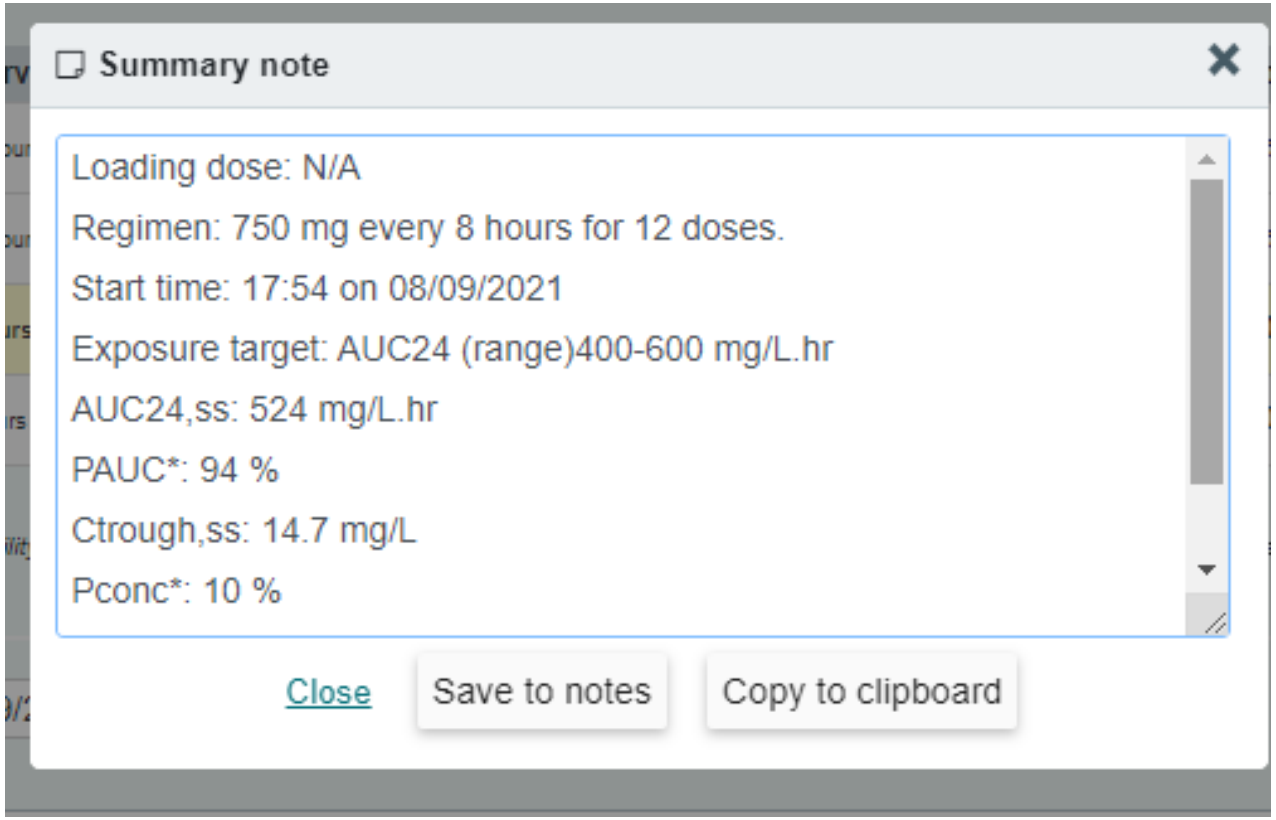
Model Analysis

- Visual changes overtime
  - Based on the closest selected model



Documentation

- Adjust and copy calculations into your progress note



Technical Considerations

- HIPAA
  - Contains patient data so platform needs to secure
- Relies on medication administration interface for key data
  - HL7 vs Flatfile setup
  - How often is data exchanged (real-time vs daily)
- Understand settings that impact recommendations made
  - E.g. dose rounding

Vancomycin regimen settings

Va1	**Available Dosing Intervals** Check all intervals to be included in the platform when selecting vancomycin dosing regimens. The standard setting includes: Q6H, Q8H, Q12H, Q24H, Q36H, Q48H *Users will only see the selected intervals.*	Choose the standard setting, or manually select intervals to be included: Standard setting ☐ Q4H ☒ Q8H ☒ Q24H ☒ Q6H ☒ Q12H ☐ Q36H ☐ Q18H ☒ Q48H
Va2	**Preferred Dosing Interval** *(choose one)*	Q12H (standard) *(if other):* every _____ hours

Implementation Challenges

Implementation Challenges

- COVID-19-related
  - Furloughs
  - Increased patient census
  - Vaccine rollout
- Hospital resource-related
  - EMR continuity
  - After-hours coverage
  - Data validation for software
  - Limited clinical staff

Implementation Challenges

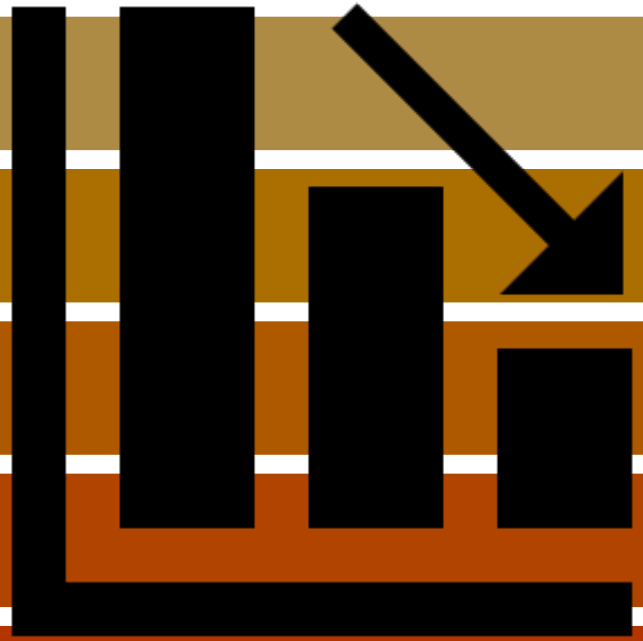
- Education-related
  - Pharmacists with different levels of training and experience
  - Pharmacy to dose vancomycin in ALL patients
  - Hospitals with and without ID services

Implementation Challenges

- Informatics-related
  - Use integrated data when possible
    - Adjusted infusion length to come from interfaced order
    - Using calculated interval vs ordered interval
  - Ensure outage training for rare interface downtimes
  - Have system pharmacy operational leads engaged in build and training design

Outcomes Evaluation In Progress

- AKI Rates
- Drug Concentrations
- Drug Utilization
- Mortality
- Length of Stay
- Process Feedback



Case Study

Happy Days Hospital is a 35-bed critical access hospital which is part of a 12-hospital health-system. They have no clinical pharmacist or infectious diseases experts, but they do have a system antimicrobial stewardship committee. They have an integrated EMR/clinical decision support since they are part of the health-system. The inpatient pharmacy is open daily from 0700 – 1900 with after hours coverage by a sister hospital.

What are the barriers for implementing vancomycin AUC monitoring with Bayesian software?

Summary

- Implementation of AUC monitoring is possible…even during a pandemic
- Create an implementation plan
- Buy-in from leadership, stewardship, and informatics teams is required
- Bayesian software is a crucial tool for AUC monitoring
- Completing a break-even analysis, securing buy-in, and thorough staff training and education are critical steps for success

Self Assessment #1

Before proposing the purchase of Bayesian software to hospital leadership, what is the best way to prepare?

A. Develop educational material for pharmacy staff
B. Conduct a break-even analysis
C. Draft AUC monitoring guidelines
D. Pray or Meditate

Self Assessment #2

Which step is necessary after implementation of Bayesian software and vancomycin AUC monitoring?

A. Nursing education
B. Pharmacist education
C. Process evaluation
D. Software data validation

Self Assessment #3.
Which of the following is a common limitation to implementing vancomycin AUC monitoring in small, independent, rural hospitals?

A. Lack of buy-in from hospital leadership
B. Lack of internet access
C. Presence of rodents in the hospital
D. Lack of infectious disease expertise

Self Assessment #4

The most efficient vancomycin dosing software setup will:

A. Avoid using population modeling
B. Use data daily
C. Integrate patient data directly from the electronic health record
D. Exclude patient data for security reasons

Questions