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It's About Time: Impact of Vancomycin AUC Dosing on Patient Outcomes & Pharmacy Workflow

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Disclosures

The presenters have no real or perceived conflicts of interest related to content in this presentation

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Learning Objectives

1. Identify key stakeholders for transitioning to a vancomycin area under the curve (AUC) dosing strategy
2. Recall how a vancomycin AUC dosing approach can improve patient outcomes
3. Recognize areas within a department or facility where implementing a vancomycin AUC approach may help to improve workflows and reduce expenses

Definitions

- MIC = minimum inhibitory concentration
  - Lowest concentration of drug needed to prevent visible growth of an organism
- AUC = area under the curve
  - Area under concentration-time curve for antimicrobials – drug activity related to total exposure of the drug
- Trough level
  - Concentration of drug in body before the next dose is administered. Often used in drug monitoring after a drug has reached steady state in body
- MRSA = methicillin-resistant *staphylococcus aureus*
  - Pathogenic organism resistant to several key antibiotics

Vancomycin

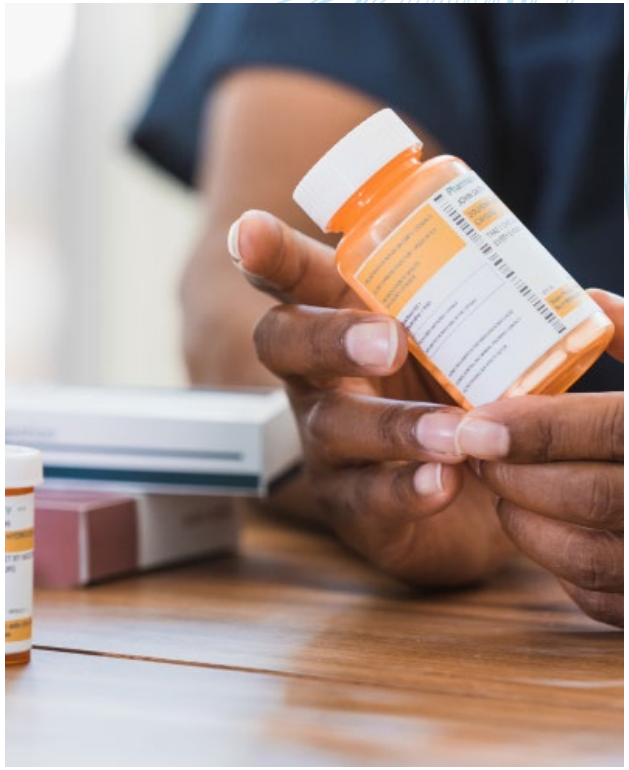
- Glycopeptide Antibiotic
- Works by inhibiting cell wall synthesis
- Often considered first-line for MRSA infections
- Notable adverse effects:
  - Nephrotoxicity
  - Ototoxicity
  - Vancomycin infusion reaction

Source: Getty Images. Used with permission of HealthTrust.

Source: Vancomycin. In: Clinical Pharmacology [database on the Internet]. Tampa (FL): Elsevier. 2024 [cited 2024 May 3]. Available from: www.clinicalpharmacology.com. Subscription required to view.

Vancomycin Pharmacokinetics

- Pharmacokinetics (PK): what occurs to a medication when it enters the body (i.e., absorption, distribution, metabolism, excretion)
- Vancomycin widely distributed into most body tissue
  - Variable lung & central nervous system penetration
- Primarily eliminated unchanged via kidneys



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Source: Vancomycin. In: Clinical Pharmacology [database on the Internet]. Tampa (FL): Elsevier. 2024 [cited 2024 May 3]. Available from: www.clinicalpharmacology.com. Subscription required to view..

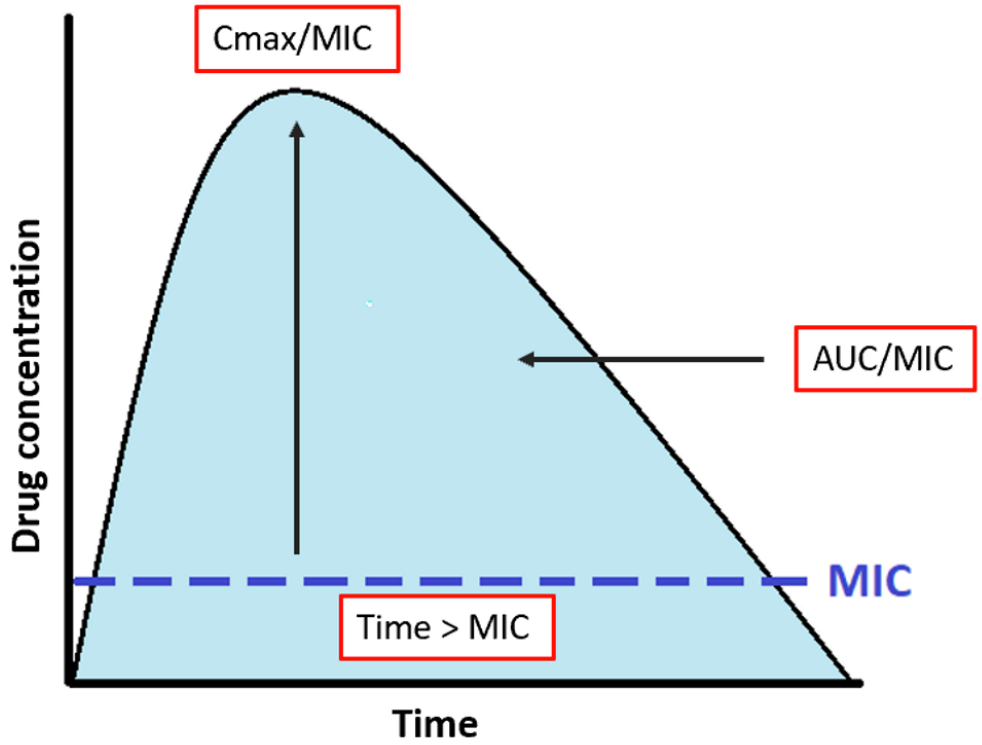
Measuring Antimicrobial Efficacy

- Goal of any antimicrobial is to effectively remove infection
- Often measured through relationship with minimum inhibitory concentration (MIC)
  - Lowest concentration of drug needed to prevent visible growth of an organism
- Historically 3 parameters are commonly used to predict efficacy

Time > MIC	Maximal activity when concentrations remain above the MIC for specific fraction of dosing interval	Beta-lactam antibiotics
Peak/MIC Ratio	Antibacterial concentration and activity are directly related	Aminoglycoside antibiotics
AUC/MIC Ratio	Activity related to total exposure	**Vancomycin**

What is AUC Dosing?

- AUC = Area Under the Curve
- Represents the area under the concentration-time curve of antimicrobials
- Goal is to have AUC over the minimum inhibitory concentration (MIC)
- Since MRSA MIC is 1 mcg/mL in > 90% of cases, historically an **AUC/MIC = AUC/1 = AUC**



Source: Graphic from: https://www.idstewardship.com/curve-enthusiasm-auc-guided-vancomycin-dosing-monitoring/. Accessed 5/17/2024

AUC Dosing – Trapezoidal vs. Bayesian

Trapezoidal Calculation

- Requires 2 levels for calculation
- Peak 1–2h after infusion has finished
- Trough 1h before next dose in same dosing interval
- Needs to be drawn at steady state
- Need to repeat process when renal function changes significantly

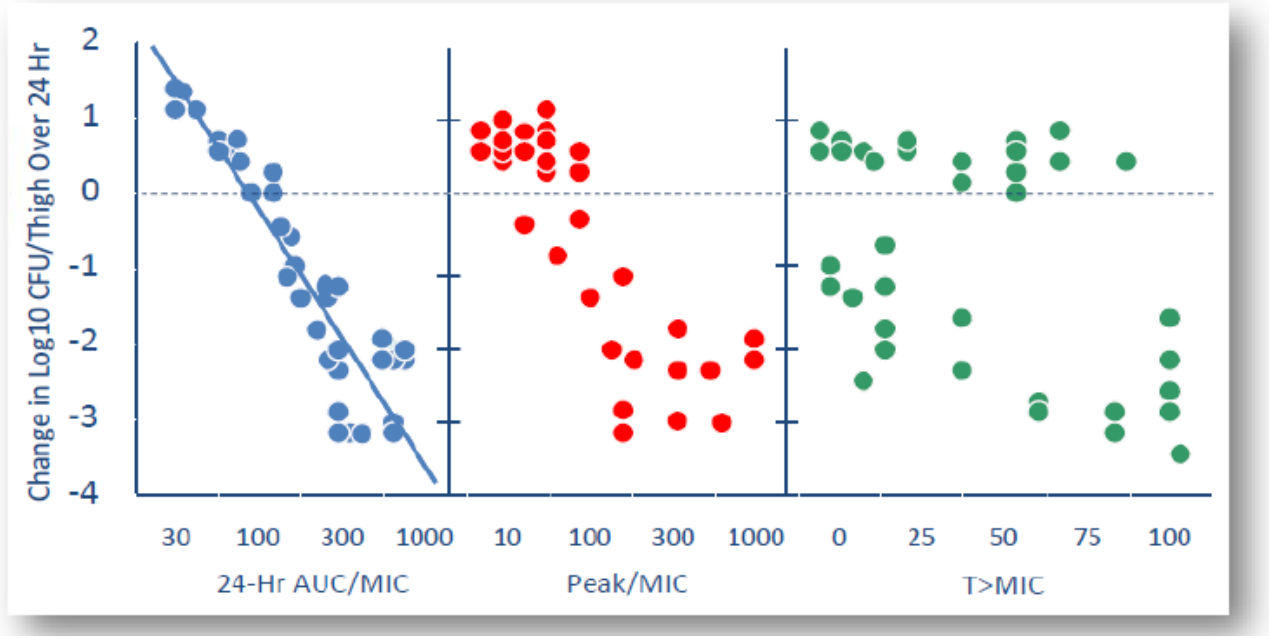
Bayesian Calculation

- Can dose with just 1 level
- More advanced calculators allow dose to be taken at any time
- Don’t need to wait for steady state
- Does not require precise timing that is seen with other methods
- Tend to see a reduction in number of lab draws & lab-related errors

Source: Chanapiwat P, Paiboonvong T, Rattanaumpawan P, Montakantikul P. Comparison of the mathematical equation and trapezoidal approach for 24 h area under the plasma concentration-time curve calculation in patients who received intravenous vancomycin in an acute care setting. Pharmacol Res Perspect. 2023 Feb;11(1):e01046. doi: 10.1002/prp2.1046. PMID: 36588162; PMCID: PMC9806189.

AUC Dosing History

- Vancomycin AUC dosing is **not** a new concept
- **1987** study by Ebert & colleagues showed AUC was the best parameter for predicting bacterial killing



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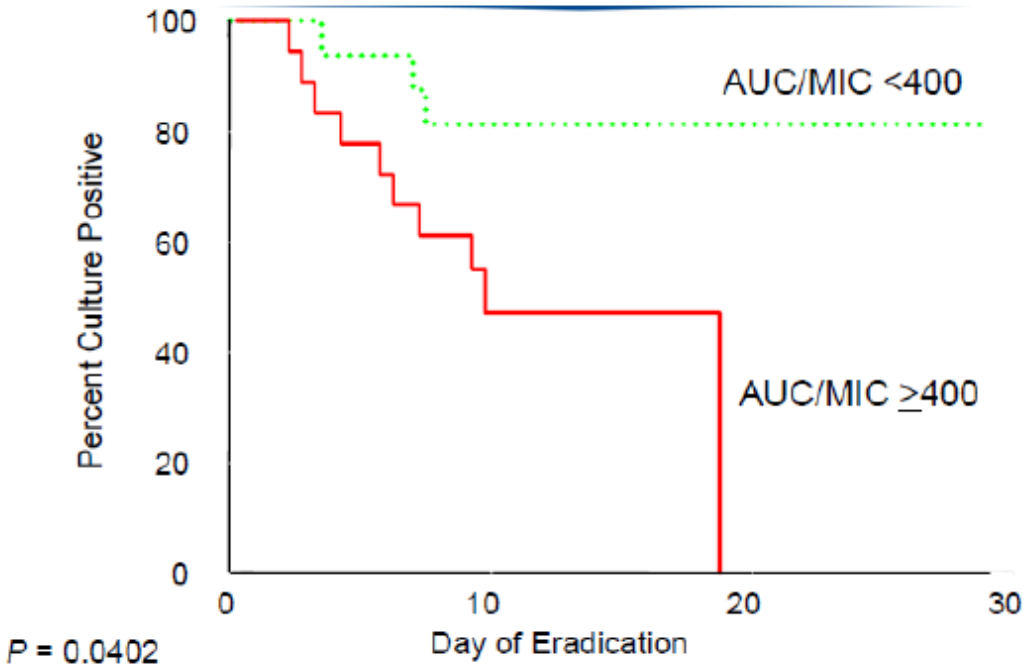
AUC Dosing History

- Specifically an AUC ≥ 400 was found to have a greater likelihood of achieving eradication of culture growth



Source: Moise-Broder PA, Forrest A, Birmingham MC, SchentagJJ. Pharmacodynamics of vancomycin and other antimicrobials in patients with Staphylococcus aureus lower respiratory tract infections. Clin Pharmacokinet. 2004;43:925-942

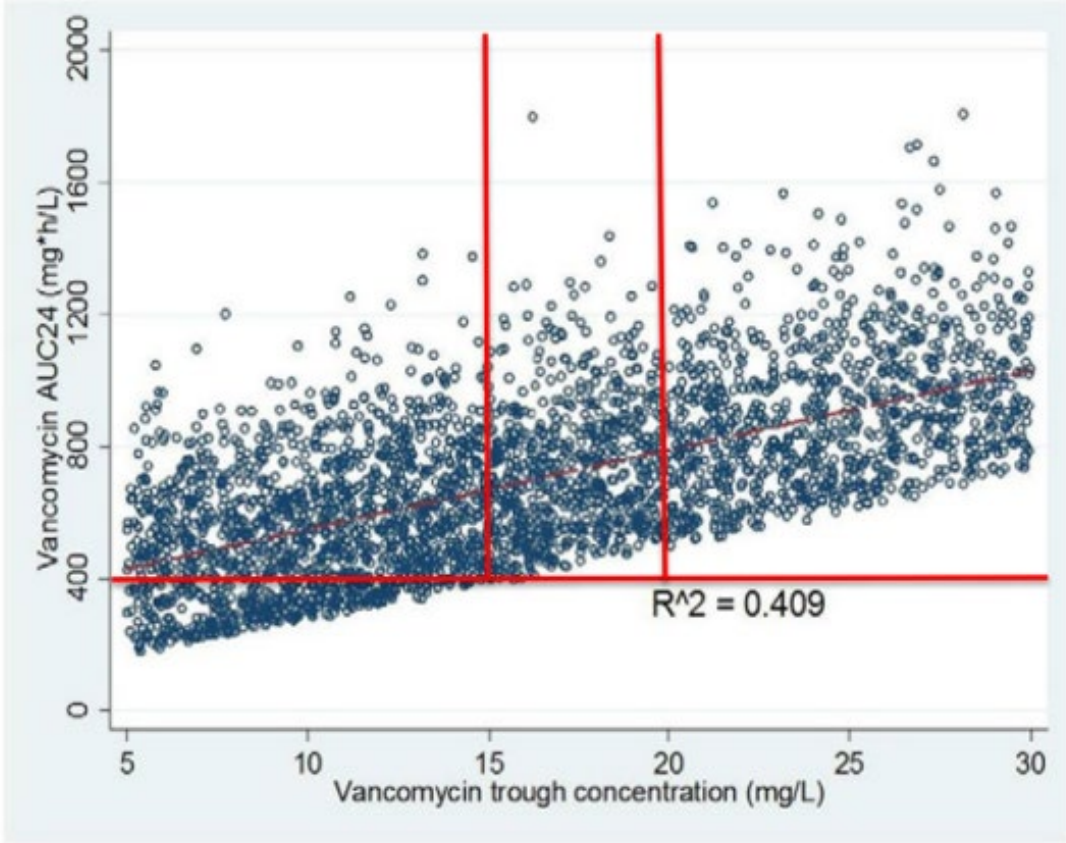
Trough Dosing History

- Vancomycin first released in 1958
- Monitoring levels was not widespread practice until the early 2000s
- Increasing doses to overcome resistant pathogens along with increasing incidents of nephrotoxicity drove desire for monitoring
- First guidelines on monitoring in 2009 – knew AUC dosing was best but calculations were near impossible for most hospital pharmacists

Source: Rubinstein E, Keynan Y. Vancomycin revisited - 60 years later. Front Public Health. 2014 Oct 31;2:217. doi: 10.3389/fpubh.2014.00217. PMID: 25401098; PMCID: PMC4215627.

Trough Dosing & AUC

- 2009 guidelines recommended troughs as surrogate marker for AUC
- 2014 study showed ~ 60% of patients with an AUC > 400 did **not** have a trough ≥ 15 mg/L
- Authors concluded “one **cannot rely solely** on the vancomycin ‘15–20 mg/L’ trough concentration range to achieve an AUC/MIC ≥ 400”



Source: Pai MP, Neely M, Rodvold KA, Lodise TP. Innovative approaches to optimizing the delivery of vancomycin in individual patients. Adv Drug Deliv Rev. 2014 Nov 20;77:50-7. doi: 10.1016/j.addr.2014.05.016. Epub 2014 Jun 5. PMID: 24910345.

Trough Dosing & Outcomes

- 2016 meta-analysis of 19 trials (2,344 patients) showed **no difference** in clinical success or mortality when comparing high (≥ 15 mg/L) & low (< 15 mg/L) troughs

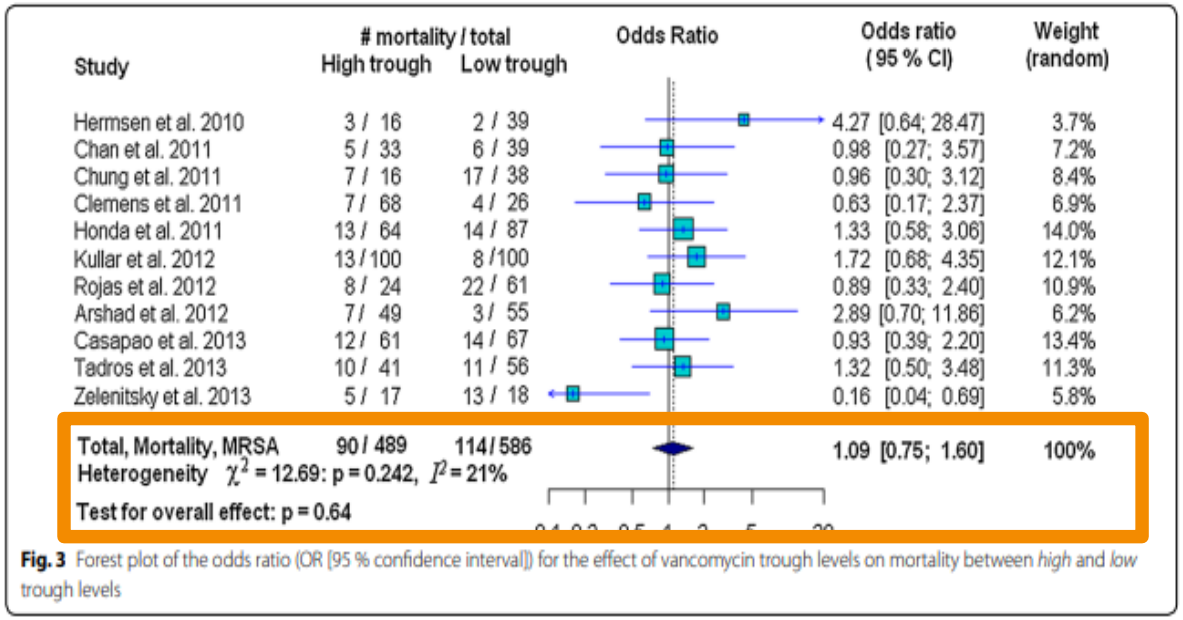


Fig. 3 Forest plot of the odds ratio (OR [95 % confidence interval]) for the effect of vancomycin trough levels on mortality between *high* and *low* trough levels

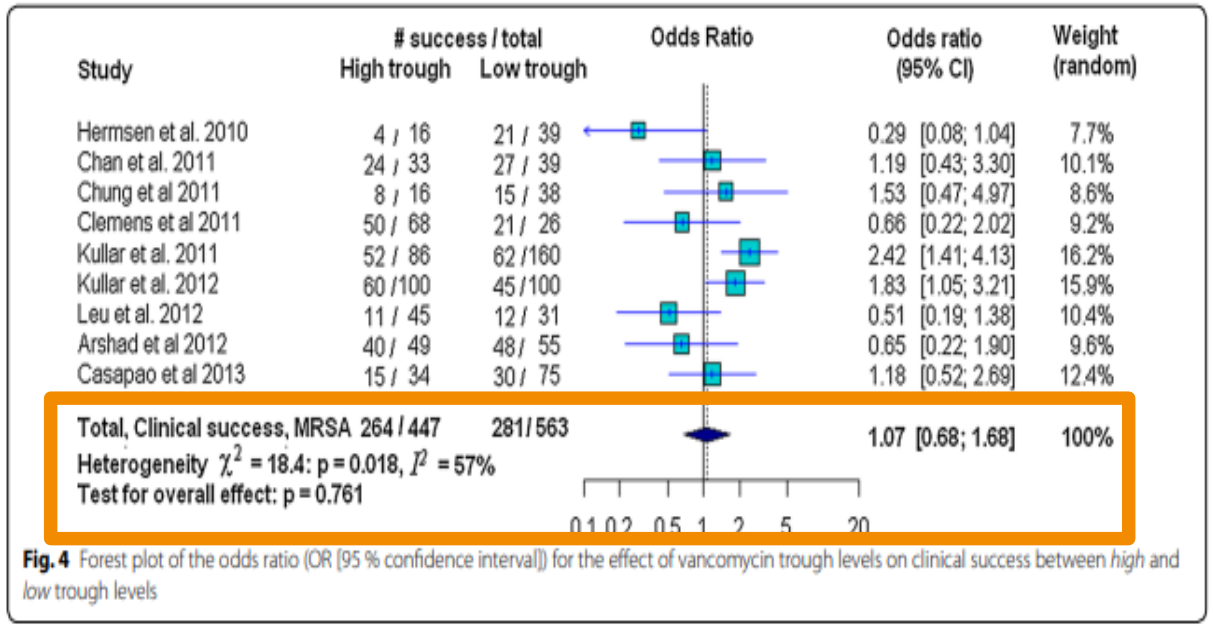


Fig. 4 Forest plot of the odds ratio (OR [95 % confidence interval]) for the effect of vancomycin trough levels on clinical success between *high* and *low* trough levels

Source: Tongsai, S., Koomanachai, P. The safety and efficacy of high versus low vancomycin trough levels in the treatment of patients with infections caused by methicillin-resistant Staphylococcus aureus: a meta-analysis. BMC Res Notes 9, 455 (2016). https://doi.org/10.1186/s13104-016-2252-7.

Trough Dosing & Nephrotoxicity

- High troughs (≥ 15 mg/L) associated with a 2–3x higher risk of nephrotoxicity

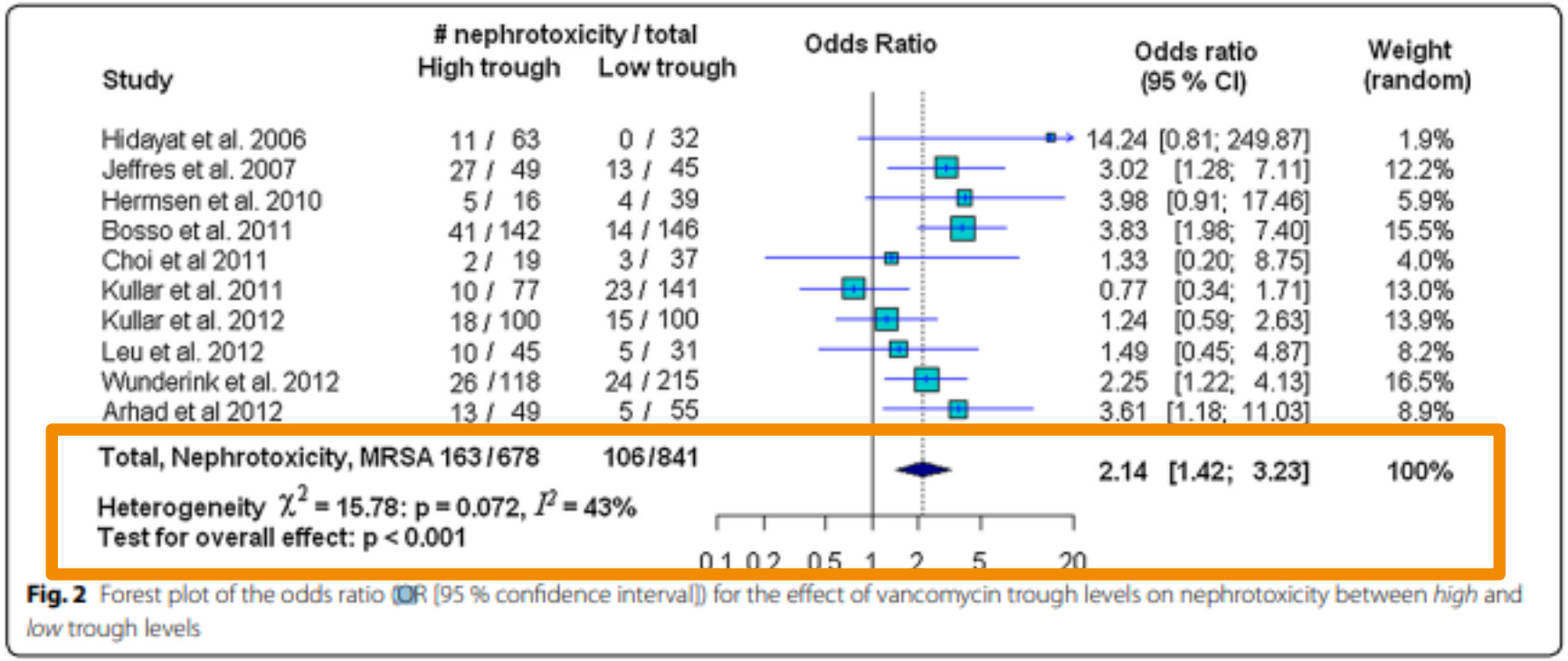


Fig. 2 Forest plot of the odds ratio (OR [95 % confidence interval]) for the effect of vancomycin trough levels on nephrotoxicity between *high* and *low* trough levels

Source: Tongsai, S., Koomanachai, P. The safety and efficacy of high versus low vancomycin trough levels in the treatment of patients with infections caused by methicillin-resistant Staphylococcus aureus: a meta-analysis. BMC Res Notes 9, 455 (2016). https://doi.org/10.1186/s13104-016-2252-7.

Comparison of Vancomycin Guidelines

2009 Guidelines

- Emphasized **trough goal** 10-20 mcg/mL
- Troughs used as surrogate markers for AUC > 400 mcg*h/mL
- Difficulties performing AUC monitoring at the time

2020 Guidelines

- Emphasized AUC goal of 400 – 600 mcg*h/mL
- Troughs have poor correlation with AUC and no longer recommended
- AUC monitoring more readily available due to technology

Source: Michael J. Rybak, Ben M. Lomaestro, John C. Rotscahfer, Robert C. Moellering, Willam A. Craig, Marianne Billeter, Joseph R. Dalovisio, Donald P. Levine, Vancomycin Therapeutic Guidelines: A Summary of Consensus Recommendations from the Infectious Diseases Society of America, the American Society of Health-System Pharmacists, and the Society of Infectious Diseases Pharmacists, Clinical Infectious Diseases, Volume 49, Issue 3, 1 August 2009, Pages 325–327, https://doi.org/10.1086/600877

Source: Michael J Rybak, Jennifer Le, Thomas P Lodise, Donald P Levine, John S Bradley, Catherine Liu, Bruce A Mueller, Manjunath P Pai, Annie Wong-Beringer, John C Rotschafer, Keith A Rodvold, Holly D Maples, Benjamin Lomaestro, Therapeutic Monitoring of Vancomycin for Serious Methicillin-resistant Staphylococcus aureus Infections: A Revised Consensus Guideline and Review by the American Society of Health-system Pharmacists, the Infectious Diseases Society of America, the Pediatric Infectious Diseases Society, and the Society of Infectious Diseases Pharmacists, Clinical Infectious Diseases, Volume 71, Issue 6, 15 September 2020, Pages 1361–1364, https://doi.org/10.1093/cid/ciaa303

Assessment Question #1

An AUC of what range is associated with a greater likelihood of clinical success with MRSA?

A. 100 – 300

B. 200 – 300

C. 400 – 600

D. > 1000

Assessment Question #1: Correct Answer

An AUC of what range is associated with a greater likelihood of clinical success with MRSA?

A. 100 – 300

B. 200 – 300

C. 400 - 600

D. > 1000

PARKLAND MEDICAL CENTER

DERRY, NH

- 86-bed community hospital
- ~ 110,000 patients in service area

Parkland Vancomycin Dosing History

- Historically used trough monitoring for all patients
- Introduction of new calculator function in 2022 allowed for AUC dosing function (trapezoidal method)
- Implemented workflow – went live with AUC dosing in November 2022
- Transitioned to new EHR in January 2023
- After 12 months post go-live did a retrospective analysis looking at 6 months pre implementation vs. 6 months post (to account for change over in EHR)

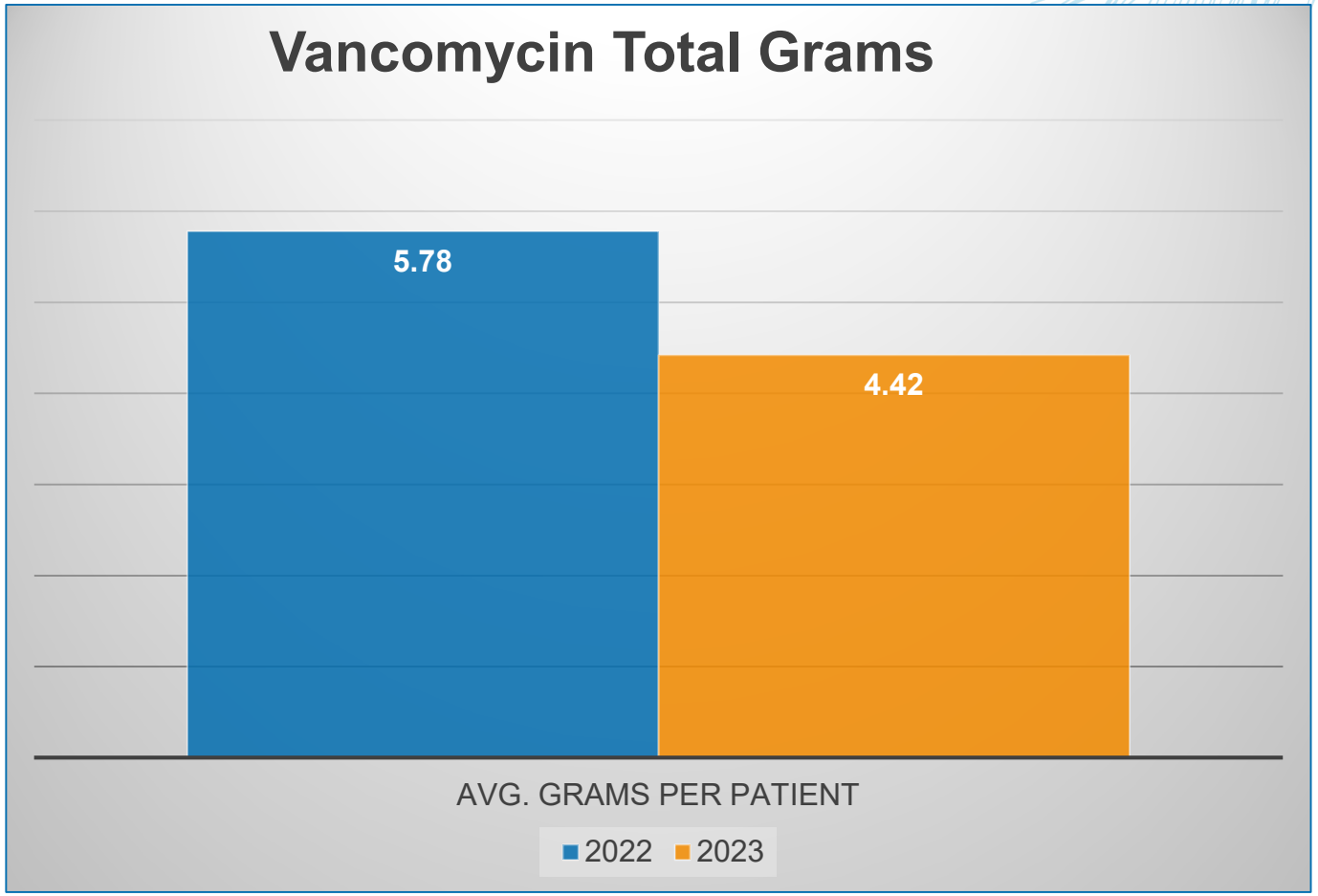
Source: Getty Images. Used with permission of HealthTrust.

Baseline Demographics – AUC Dosing

Demographic (n = 76)	# (%)
Male	45 (59.2%)
Age (avg.)	61 (29–88)
Weight (avg.)	96.4 kg (52–182)
ICU%	25 (32.9%)
Most common indication	SSTI (26.3%)
Baseline SCr	1.11 (0.52–2.16)
# of doses (avg.)	8.3 (4–63)
# of doses (median)	6

Vancomycin Dosing Breakdown

~ 23.5% less total vancomycin grams received over course of therapy



Operational Definition – AKI

AKIN Guidelines[1]

- Acute Kidney Injury Network
- Increase in Scr ≥ 0.3 mg/dL within 48h
- Increase in Scr ≥ 50% of baseline within 48h

KDIGO Guidelines[2]

- Kidney Disease: Improving Global Outcomes
- Increase in Scr ≥ 0.3 mg/dL within 48h
- Increase in Scr ≥ 50% of baseline within 7d

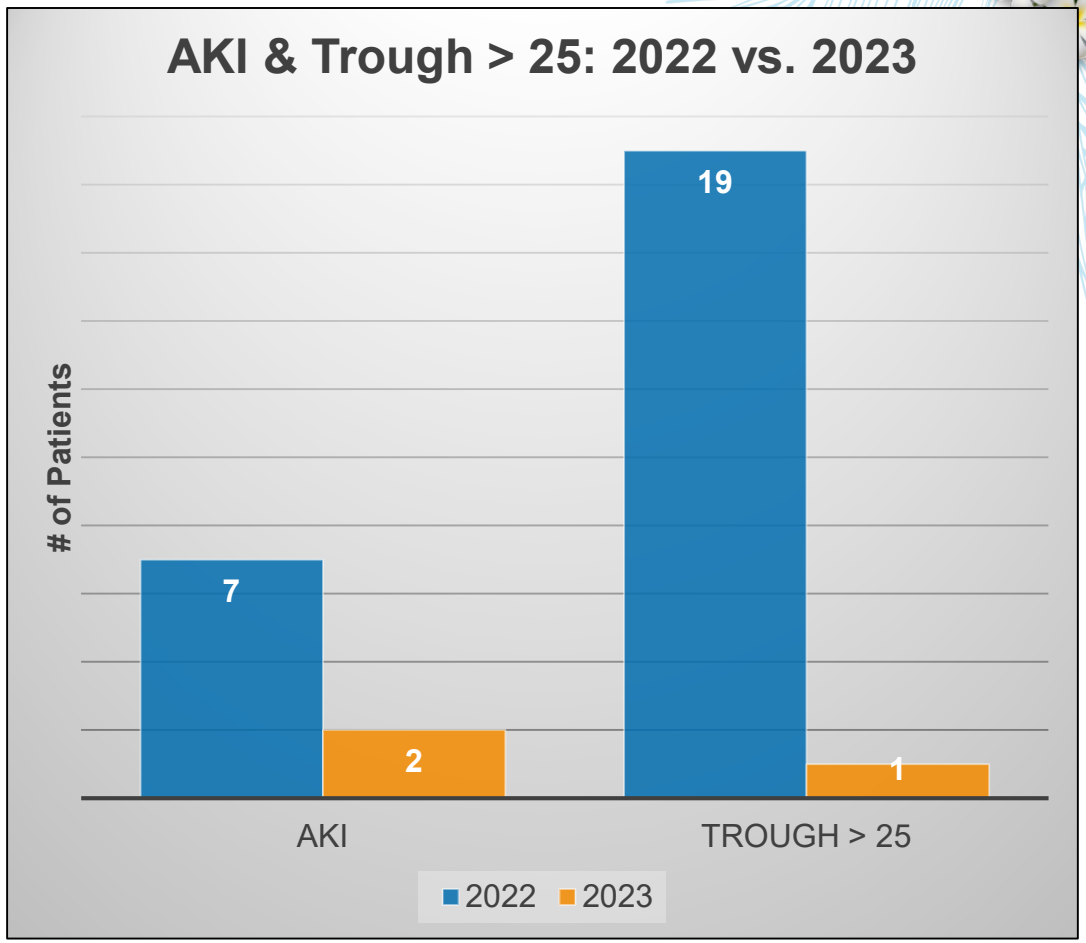
***For purposes of this analysis used Scr ≥ 50% of baseline during course of therapy as threshold**

Sources:

1. Bellomo R, Ronco C, Kellum JA, et al. Acute renal failure-definition, outcome measures, animal models, fluid therapy and information technology needs: the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. Crit Care 2004; 8:B204. Copyright © 2004 BioMed Central Ltd.
2. Kidney Disease: Improving Global Outcomes (KDIGO). Acute Kidney Injury Work Group. KDIGO clinical practice guidelines for acute kidney injury. Kidney Int Suppl 2012; 2:1.

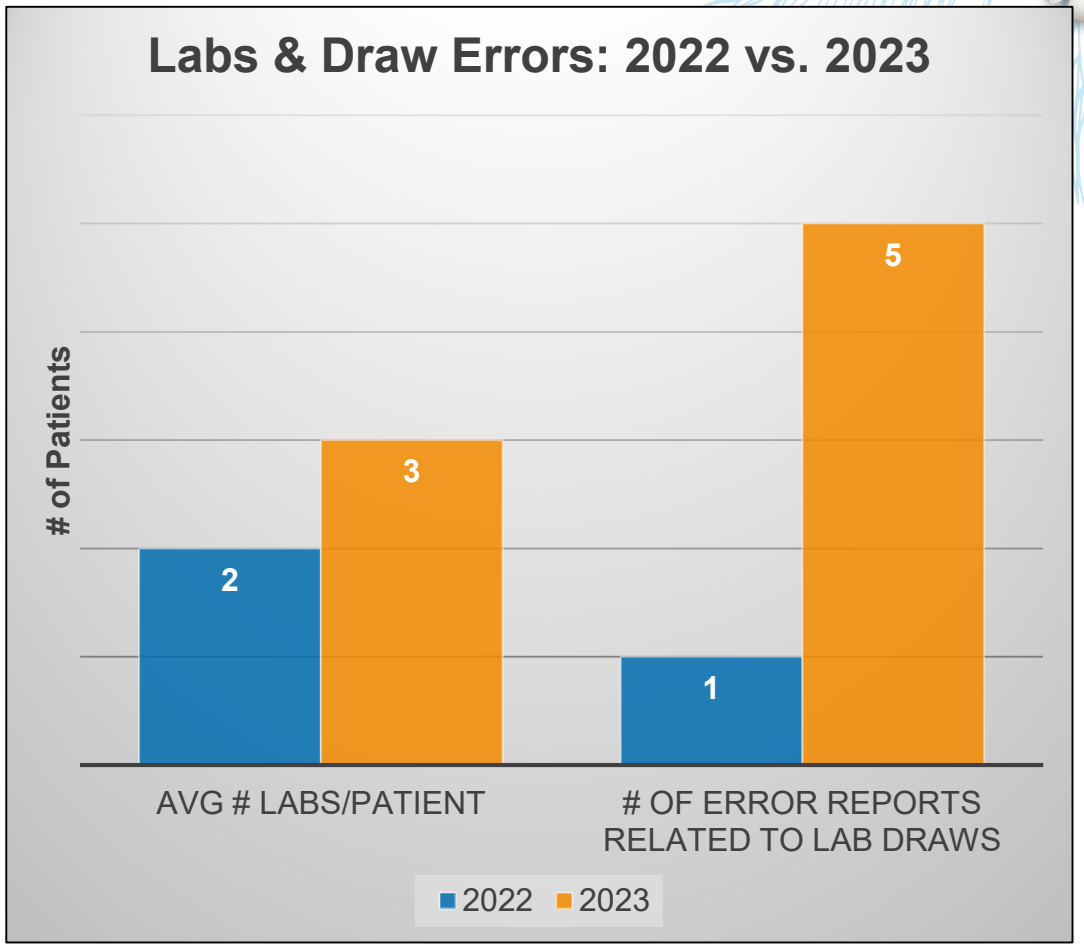
Renal Data & Trough Values

- Compared to same timeframe in 2022
- AKI: 7 (7.6%) patients in 2022 vs. 2 (2.6%) in 2023
  - **65.7% relative decrease** in AKI events
  - **AKI associated with longer LOS**: 10.68d avg. vs. 8.11d
- Trough > 25: 19 (21.1%) in 2022 vs. 1 (1.3%) in 2023
  - **93.8% relative decrease in events**



Lab Draws & Errors

- On average patients needed at least 1 additional lab draw when AUC dosing was used
- Higher rate of reported errors related to lab draws when AUC dosing was used
  - **400% increase**
  - Most common reported error was labs drawn too early or while bag was infusing
  - Errors likely more common (i.e., under-reported)



Workforce Savings

- Assumptions:
  - 5 minutes of tech time per bag at $2 per bag (~ $25/hour)
  - 1 minute of pharmacist time checking bag at $0.83 per bag (~ $50/hr)

Year	# Bags Batched/ Month	Estimated Tech Time (min.)	Estimated Pharmacist Time (min.)	Estimated Staff Cost/ Month	Avg. Savings
2022	250	1250 min. = $500	250 min. = $207.50	$700/month	NA
2023	140	700 min. = $280	140 min. = $116.20	$400/month	↓ **42.8%**

Summary – Parkland Medical Center

Positive Outcomes

- **Fewer** grams per course of therapy (~ 23% less)
- **Reduction** in AKI (2.6% in 2023 vs. 7.6% in 2022)
- **Reduction** in troughs > 25 (1.3% in 2023 vs. 21.1% in 2022)

Positive Outcomes

- **Reduction** in workforce hours used (~ 10h/month reduction between batching & checking)
- **Reduction** in workforce dollars (~ 42% reduction in workforce costs)

Cautionary Outcomes

- **Higher** rate of lab draws with AUC patients
- **Higher** rate of lab draw errors
- **Higher** learning curve for staff

Assessment Question #2

A pharmacy director wants to explore using AUC dosing for vancomycin. Who should be involved in initial discussions?

A. Lab leadership

B. Nursing leadership

C. Quality leadership

D. All of the above

Assessment Question #2: Correct Answer

A pharmacy director wants to explore using AUC dosing for vancomycin. Who should be involved in initial discussions?

A. Lab leadership

B. Nursing leadership

C. Quality leadership

D. All of the above

Assessment Question #3

If a facility is considering implementing vancomycin AUC dosing, what area(s) may see improvements in workflow?

A. Lab

B. Pharmacy

C. Environmental Services

D. Rehabilitation Unit

Assessment Question #3: Correct Answer

If a facility is considering implementing vancomycin AUC dosing, what area(s) may see improvements in workflow?

A. Lab

B. Pharmacy

C. Environmental Services

D. Rehabilitation Unit

RESEARCH MEDICAL CENTER

KANSAS CITY, MO

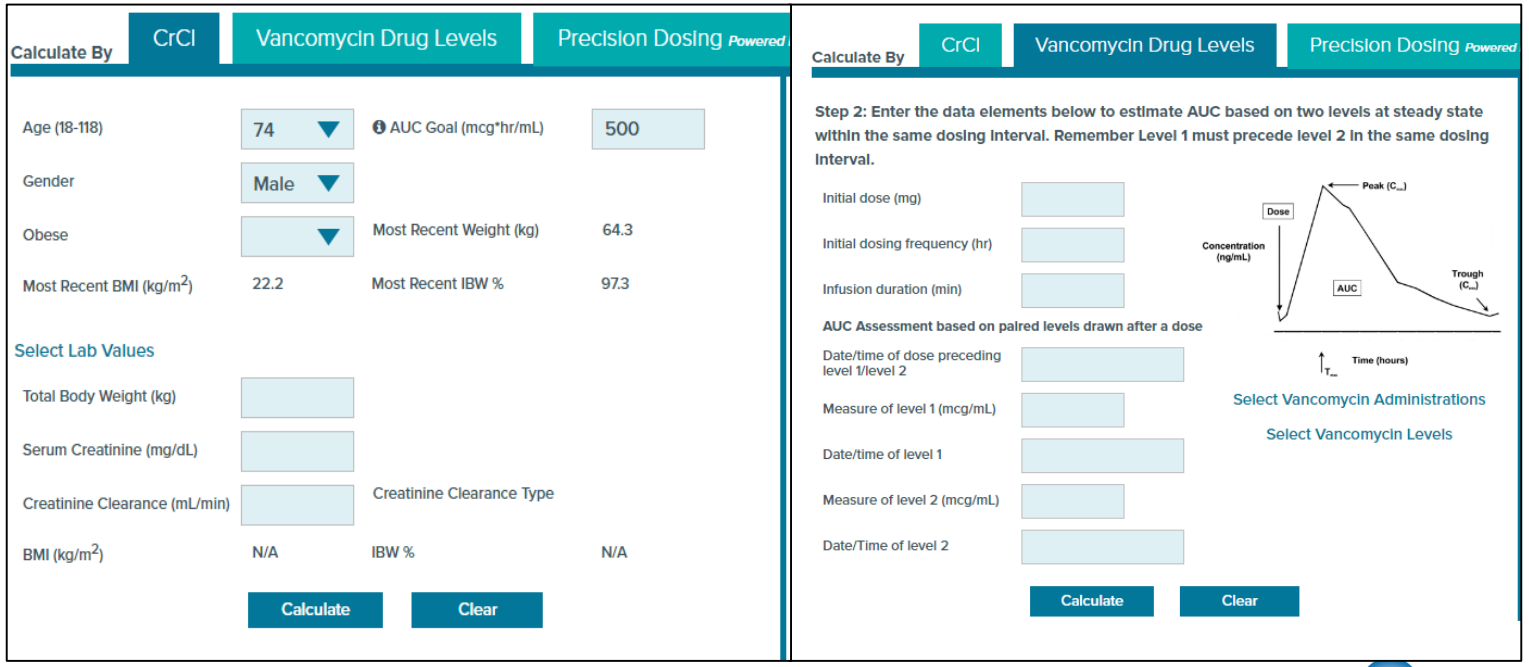
- 590-bed tertiary-care hospital
- Services included:
  - Level 1 trauma center
  - Three ICUs including neurosurgical
  - Kidney/Pancreas Transplant

Research Medical Center

- Prior to January 2021, used single level trough-based dosing
- Transitioned to two level trapezoidal-based dosing utilizing the AUC Calculator in VigiLanz (pictured below)
- Completed small retrospective review similar to Parkland involving 60 patients

Excluded if:

- < 3 days of therapy
- Not dosed by RMC pharmacist
- Dialysis patients



Baseline Demographics

Demographic	Trough (n=30)	AUC (n=30)
Male	18 (60%)	19 (63.3%)
Age (years; avg.)	64 (23–86)	55 (23–86)
Weight (kg; avg.)	87.8 (52.7 – 173.8)	87.6 (42.1 – 176.6)
ICU%	6 (20%)	11 (36.7%)
Most common indication	SSTI (36.7%)	SSTI (40%)
Baseline SCr (mg/dL; avg.)	1.07	0.96
# of doses (avg.)	10	13
# of doses (median)	7	9

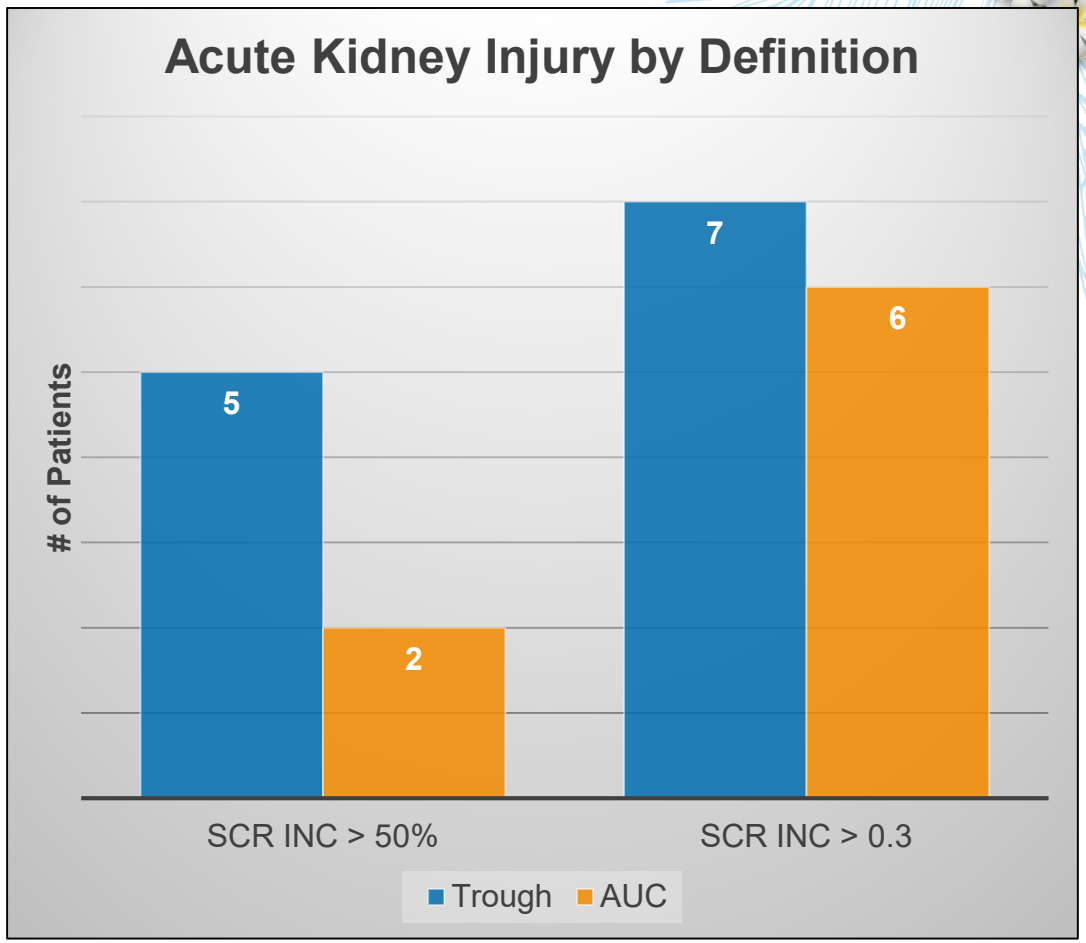
Outcomes – Total Dose & Lab Draws

Dosing Characteristic (avg.)	Trough (n=30)	AUC (n=30)
mg/day	**1919**	**2092**[1]
Doses per day	2	2
mg/kg/day	21.8	23.9
Lab draws per patient	2.2	3.4
Lab draws per day	**0.4**	**0.5**
Lab draw error (%)	**10**	**20**[2]

1. Possible reasons for similar average dosing per patient include adoption of 2500 and 3000 mg max dose options for 25 mg/kg load in AUC-based dosing
2. Included “peak” values drawn within one hour post-infusion end (distribution phase)

Outcomes – Renal Toxicity

- Evaluated AKI occurrence using two of the definitions from KDIGO
  - Controversy regarding the clinical relevance of reported AKIs in the literature (e.g., does temporary bump of 0.4 correlate with sig dec drug clearance?)
- SCr increase greater than 50%
  - **Five (16.7%) in the trough vs. 2 (6.7%) in AUC**
- SCr increase greater than 0.3 mg/dL
  - Similar between groups with 7 (22.3%) in trough vs. 6 (20%) in AUC



Source: Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group. KDIGO Clinical Practice Guideline for Acute Kidney Injury. Kidney inter., Suppl. 2012; 2:1–138.

Summary – Research Medical Center

Theoretical/Evidence-Based Assumption	Per RMC Review
1. AUC-based dosing would decrease the total amount of vanc used per patient	Slightly higher average daily dose in AUC group
2. AUC dosing would require substantially more lab draws	Interestingly, lab draws per day was virtually same in both groups
3. AUC dosing would result in more lab errors when collecting levels	AUC dosing results in twice as many lab errors (10% vs. 20 %)
4. AUC dosing would decrease risk of vancomycin-induced nephrotoxicity	There were 3 fewer (60%) AKIs (defined as SCr > 50% from baseline) in AUC dosing

Summary of Outcomes

Outcome	Parkland Medical Center	Research Medical Center
Decreased total vancomycin used	✓	✗
Decreased AKI (Scr ≥ 50%)	✓	✓
Decrease in pharmacy workforce hours	✓	N/A
Increased lab draws per patient	✓	✗
Increased lab-related errors	✓	✓

Lessons Learned

- Need buy-in from all stakeholders, including:
  - Pharmacy staff
  - Lab
  - Quality
  - Local antimicrobial stewardship team
- Prepare for staff engagement & education, especially with pharmacy/lab/nursing
- Promote change to AUC dosing as patient safety initiative
- Have touchpoints throughout the roll-out to assess program

Source: Getty Images. Used with permission of HealthTrust.

Summary

- Recent guidelines recommend vancomycin AUC dosing over trough-only approach
- Several studies have shown AUC dosing correlates with improved patient outcomes & reduced adverse events (specifically AKI)
- By implementing an AUC approach you **may** see
  - **Reduced** vancomycin-related AKIs
  - **Reduced** vancomycin use
  - **Improved** pharmacy workflows
- Be aware of **potential** downfalls, such as
  - Education/re-education
  - **Increase** in lab draws
  - **Increase** in lab-related errors due to new process

Source: Getty Images. Used with permission of HealthTrust.

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- Bellomo R, Ronco C, Kellum JA, et al. Acute renal failure-definition, outcome measures, animal models, fluid therapy and information technology needs: the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. Crit Care 2004; 8:B204. Copyright © 2004 BioMed Central Ltd.
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