AMERICAN UNIVERSITY OF BEIRUT MEDICAL CENTER

المركز الطبي في الجامعة الأميركية في بيروت

UPDATES IN DOSING AND MONITORING OF VANCOMYCIN BASED ON PHARMACOKINETIC CONSIDERATIONS

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DISCLOSURES

I declare to meeting attendees that there are no financial relationships with any for-profit companies that are directly or indirectly related to the subject of my presentation.

OUTLINE

1. REVIEW OF EVIDENCE FOR VANCOMYCIN THERAPEUTIC MONITORING
   - 2020 VANCOMYCIN GUIDELINES VERSUS 2009
   - TROUGH CORRELATION WITH AREA UNDER THE CURVE (AUC)
   - REVIEW OF EFFICACY DATA
   - REVIEW OF SAFETY DATA
2. PRACTICAL RECOMMENDATIONS FOR AUC-GUIDED VANCOMYCIN MONITORING STRATEGY
3. IMPLEMENTATION OF AUC-GUIDED MONITORING STRATEGY
   - EXPERIENCE AT AUBMC
   - CHALLENGES AND SUGGESTED SOLUTIONS

VANCOMYCIN MONITORING - HISTORICALLY

- ASHP 2009 Vancomycin Therapeutic Monitoring Guidelines:
  - Single trough concentration before 4th dose.
  - Steady state target trough of 15-20 mg/L:
    - Complicated *Staphylococcus aureus* infections
    - Deep seated infections (meningitis, osteomyelitis, endocarditis, pneumonia)

➡ To achieve an area under the curve **AUC ≥ 400** in most patients when *S. aureus* vancomycin **MIC≤ 1 mg/L**

Rybak M et al. *Am J Health-Syst Pharm.* 2009; 66:82-98

RATIONALE BEHIND TROUGH-BASED MONITORING

- AUC was seen as an impractical tool to use at the bedside with a need of intensive sampling or use of a software
- Mathematical assumption: maintaining a trough ≥ 15 mg/L would ensure an AUC ≥ 400 mg*L/h in most patients
- Hence, the trough was used as an AUC surrogate for improved efficacy in serious methicillin-resistant *S. aureus* (MRSA) infections

However…

Rybak M et al. *Am J Health-Syst Pharm.* 2009; 66:82-98. Rybak MJ et al. *Am J Health-Syst Pharm.* 2020; 77(11):835-864

VANCOMYCIN MONITORING – UPDATES

- ASHP 2020 Vancomycin Therapeutic Drug Monitoring Guidelines:
  - Switch from trough-based to AUC-based monitoring
  - **Target AUC 400-600 mg*h/L** for serious MRSA infections

(MIC = 1 mg/L)

- **1-2 post-dose levels** within the first 24 – 48 hours (Bayesian approach)

OR

- **2 post-dose concentrations** at steady state (first order pharmacokinetics/trapezoidal rule)

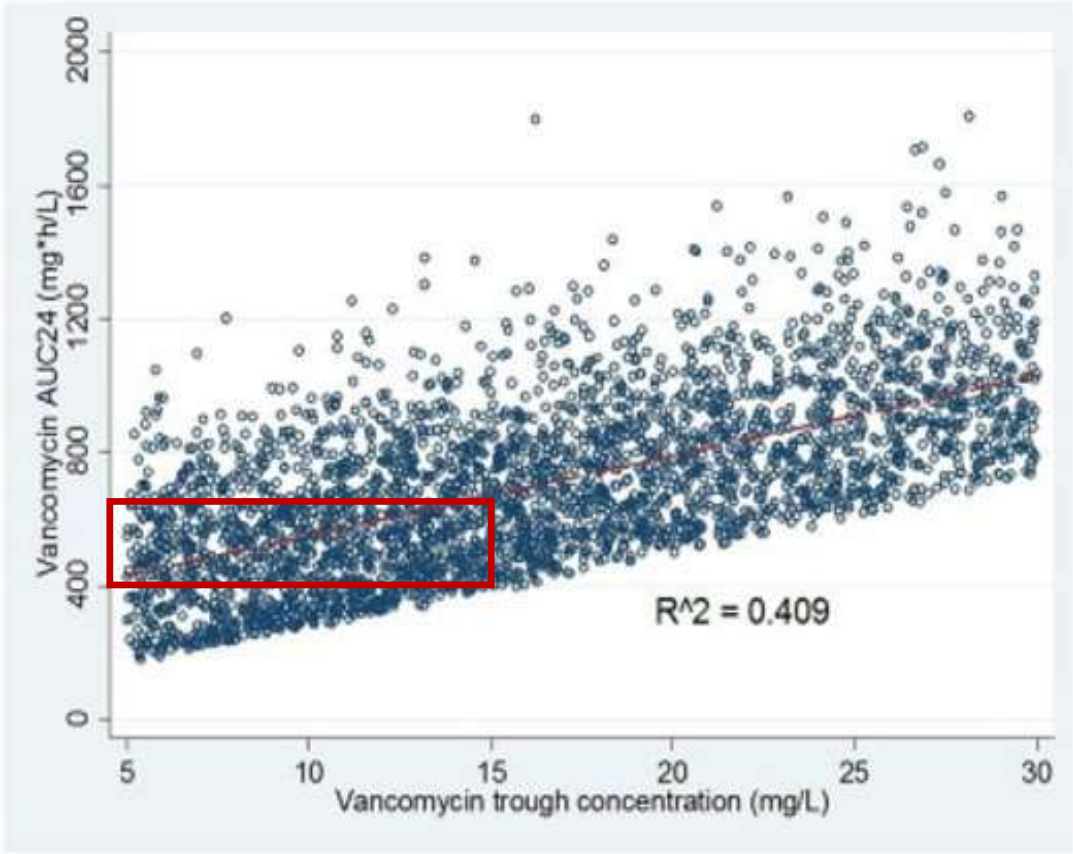
Rybak MJ et al. *Am J Health-Syst Pharm.* 2020; 77(11):835-864

TROUGH VERSUS AUC-BASED MONITORING AND VANCOMYCIN EFFICACY

- Preclinical and clinical data from *S. aureus* bacteremia & pneumonia indicate: **AUC/MIC > 400 mg*h/L** promotes treatment success

- A meta-analysis consistent of many observational studies:
  - Trough concentrations > 15 mg/L do **NOT** predict efficacy and are not associated with significantly reduced treatment failure, persistent bacteremia, or mortality

Prybylski JP. *Pharmacotherapy*. 2015;35(10):889-898



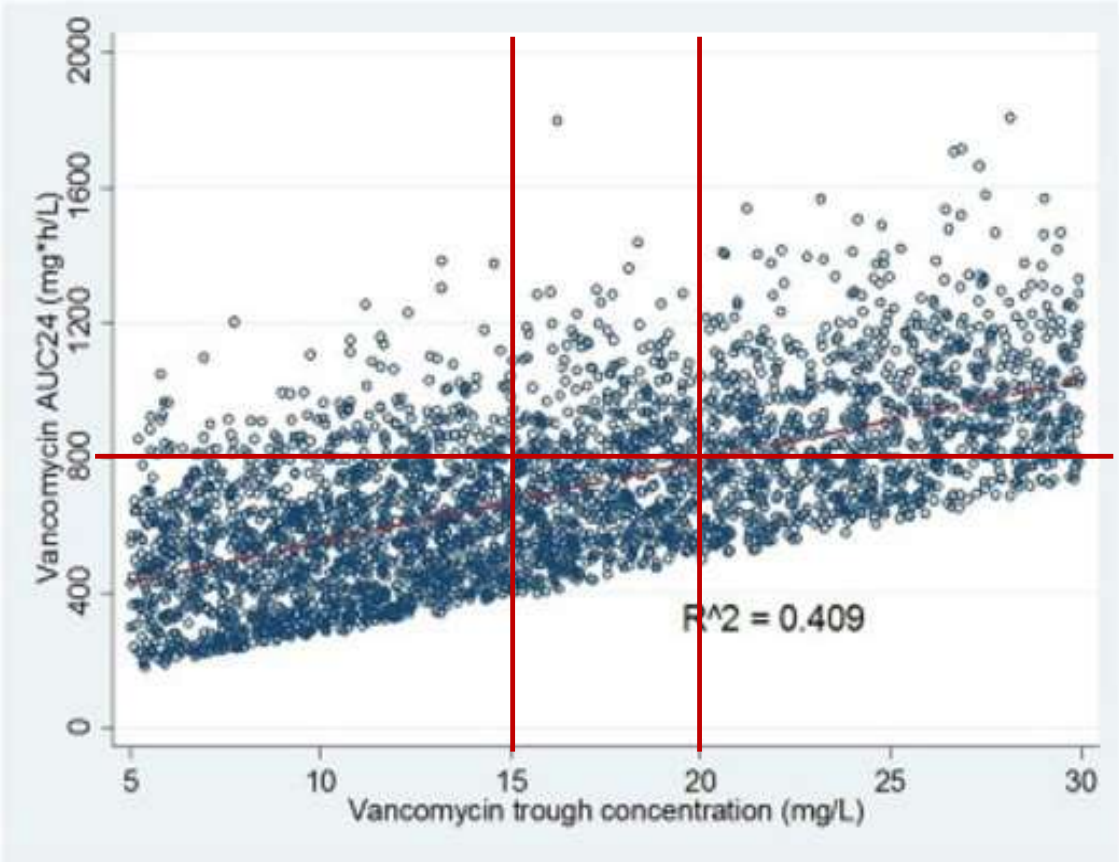
AUC24h versus trough vancomycin concentration from 5000 subjects using Monte Carlo simulation

CORRELATION BETWEEN TROUGH AND AUC

- One trough value can yield vastly different AUC values
- More than 50% of adults with AUC ≥ 400 mg*L/h have **trough concentrations < 15 mg/L**
- Hence, the trough correlates badly with AUC

Pai MP, et al. *Adv Drug Deliv Rev*. 2014;77:50-57

TROUGH AND AUC-BASED MONITORING AND VANCOMYCIN SAFETY



- Multiple studies demonstrated nephrotoxicity is associated with:
  - Trough concentrations > 15 mg/L
  - AUC values > 600-800 mg*h/L

Zasowski EJ et al. *Antimicrob Agents Chemother*. 2017; 62(1):e01684-17; Pai MP, et al. *Adv Drug Deliv Rev*. 2014;77:50-57

LIMITATIONS OF THE TROUGH-BASED APPROACH

- Newer evidence shows that there is a poor correlation between AUC and trough values, and that there may be more nephrotoxicity with troughs>15, with no evidence of better clinical outcomes
- Difficult to achieve pre-specified trough targets
  - Numerous modifications to dosing regimen to reach 15-20 mg/L range and maintain concentration in this narrow interval

Kishk O.A.et.al. *J Pediatr Pharmacol Ther* 2017, Seabury R.W.et.al. *Annals of Pharmacotherapy* 2017, Stoessel, A.M., et.al. *Journal of Pharmacy Practice* 2018

BENEFITS OF THE AUC-BASED APPROACH

- 50% relative reduction in vancomycin nephrotoxicity
- Improved vancomycin associated cure rates
- Cost savings of 846 USD per patient encounter compared to trough-based monitoring

Lodise TP et al. Clin Infect Dis. 2014; 59(5):666-675; Finch NA et al. Antimicrobial Agents Chemother. 2017; 61(12): e01293-17; Lee BV et al. Clin Microbial Infections. 2021; 27(9): 1346.e1-1346.e7

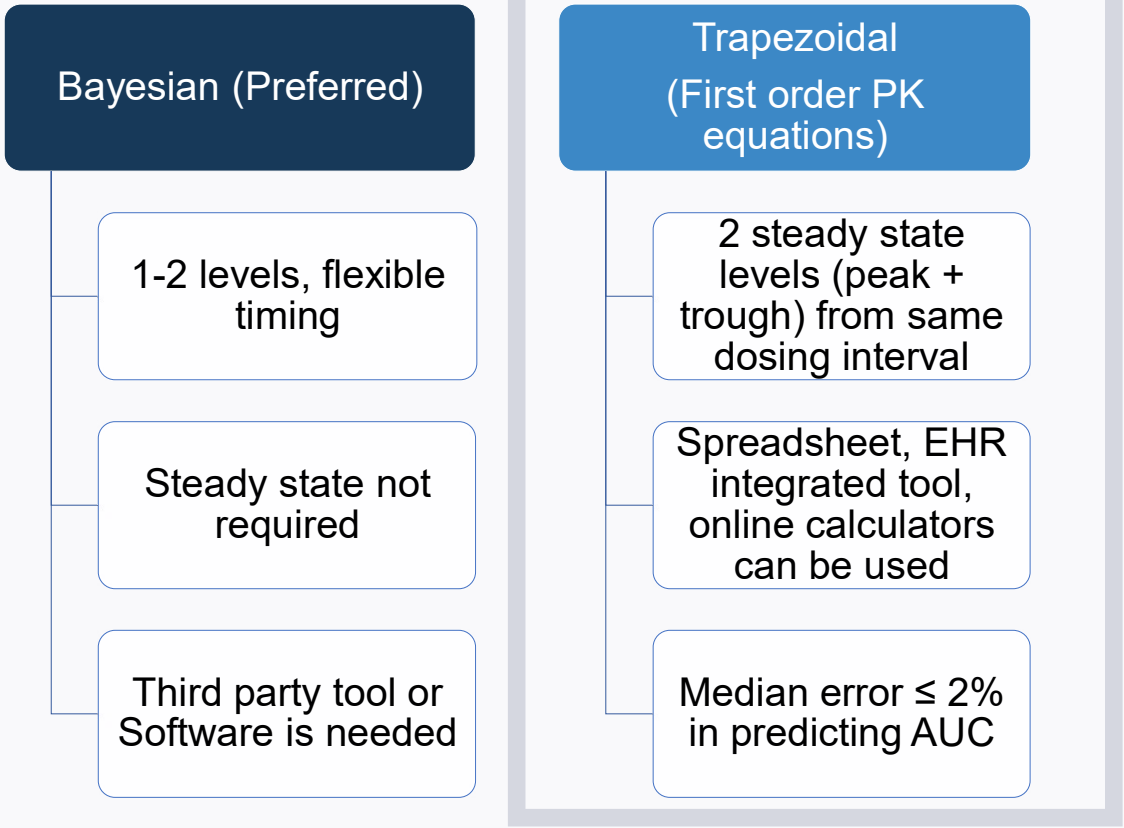
PATIENT ELIGIBILITY

- Adult and pediatric patients maintained on vancomycin therapy are eligible
- Evidence is mostly available for treatment of MRSA
- Patients with the following are excluded:
  - Anticipated short duration of treatment
    - Surgical prophylaxis
  - Unstable renal function
    - Intermittent hemodialysis
    - Peritoneal dialysis
    - Acute kidney injury

Vancomycin dosing based on random levels

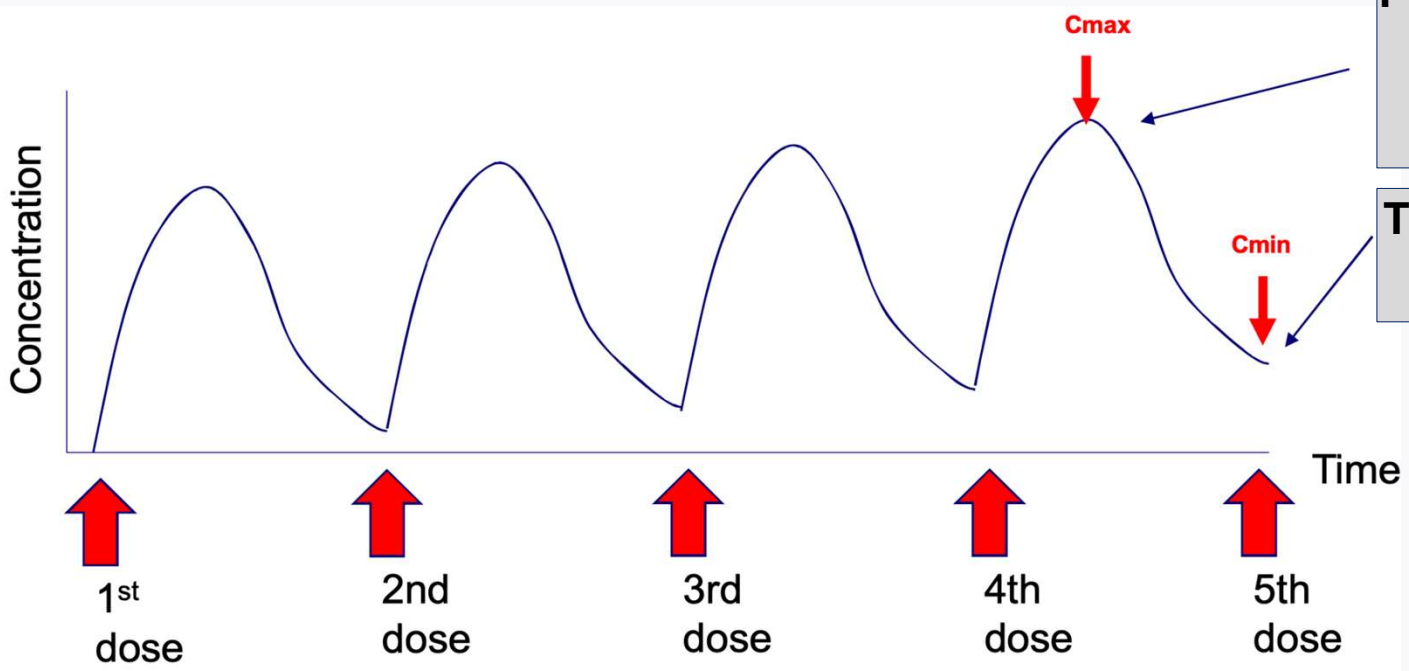
Rybak MJ et al. *Am J Health-Syst Pharm.* 2020; 77(11):835-864

VANCOMYCIN AUC ESTIMATION METHODS



Rybak MJ et al. *Am J Health-Syst Pharm.* 2020; 77(11):835-864

TRAPEZOIDAL RULE METHOD



Peak: 1-2 hours after the end of the infusion of the 4th dose

Trough: 30'-60' prior to 5th dose

Calculate AUC by plotting the levels into an EHR-integrated calculator, any other AUC calculator, or by pharmacokinetic calculations

Rybak MJ et al. *Am J Health-Syst Pharm.* 2020; 77(11):835-864

MONITORING FREQUENCY

- No need to monitor if short expected duration of therapy (≤ 3-5 days) and stable renal function
- At least two levels (1 peak and 1 trough) are recommended otherwise
  - Follow-up trough to be done at least weekly if hemodynamically stable
- Patients in need of more frequent monitoring

Fluctuating renal function/fluid balance	Concomitant nephrotoxic drugs	Older patients receiving q8h dosing or extremes of age	Not responding to initial regimen or decompensating on current regimen

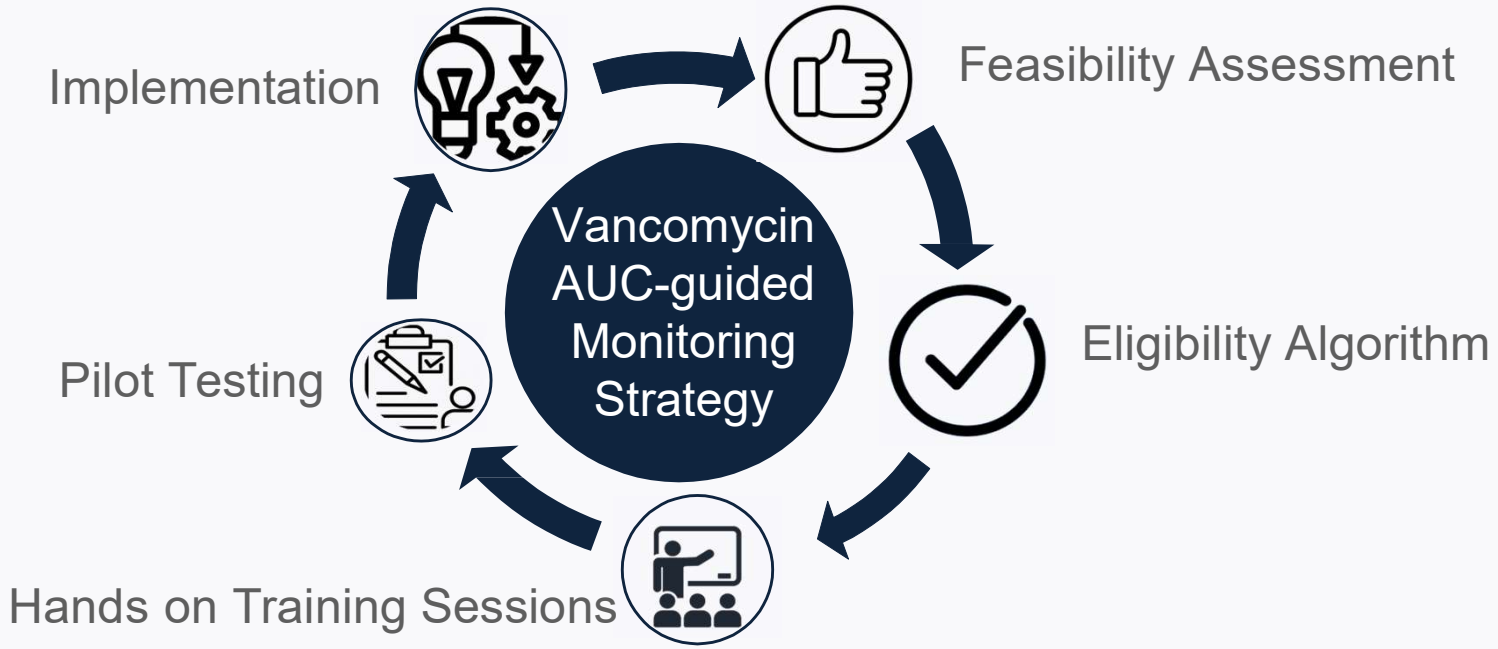
Rybak MJ et al. *Am J Health-Syst Pharm.* 2020; 77(11):835-864; Wieczorkiewicz S. M. et.al., *ASHP*. 2016

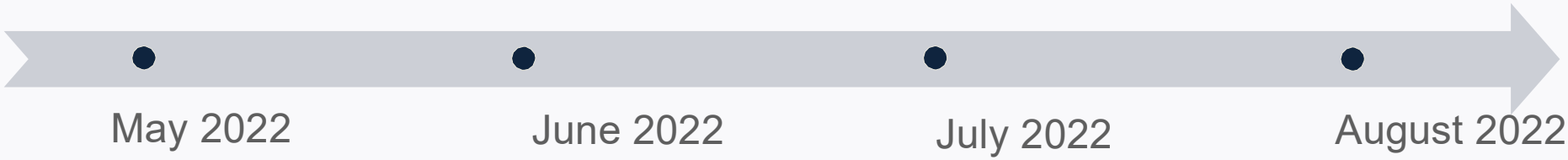
INITIAL DOSING RECOMMENDATIONS

- AUC-based estimation is recommended for initial dosing
- If unavailable, general initial dosing ranges are available in the ASHP 2020 guidelines for:
  - Adults
  - Pediatric patients with different ranges depending on age group
- Dosing Pearls
  - Use actual body weight
  - Maximal rate of infusion is 1g/h
  - Loading dose recommendations in critically ill patients

Rybak MJ et al. *Am J Health-Syst Pharm.* 2020; 77(11):835-864; Wieczorkiewicz S. M. et.al., *ASHP*. 2016

IMPLEMENTATION OF AUC-BASED VANCOMYCIN MONITORING STRATEGY





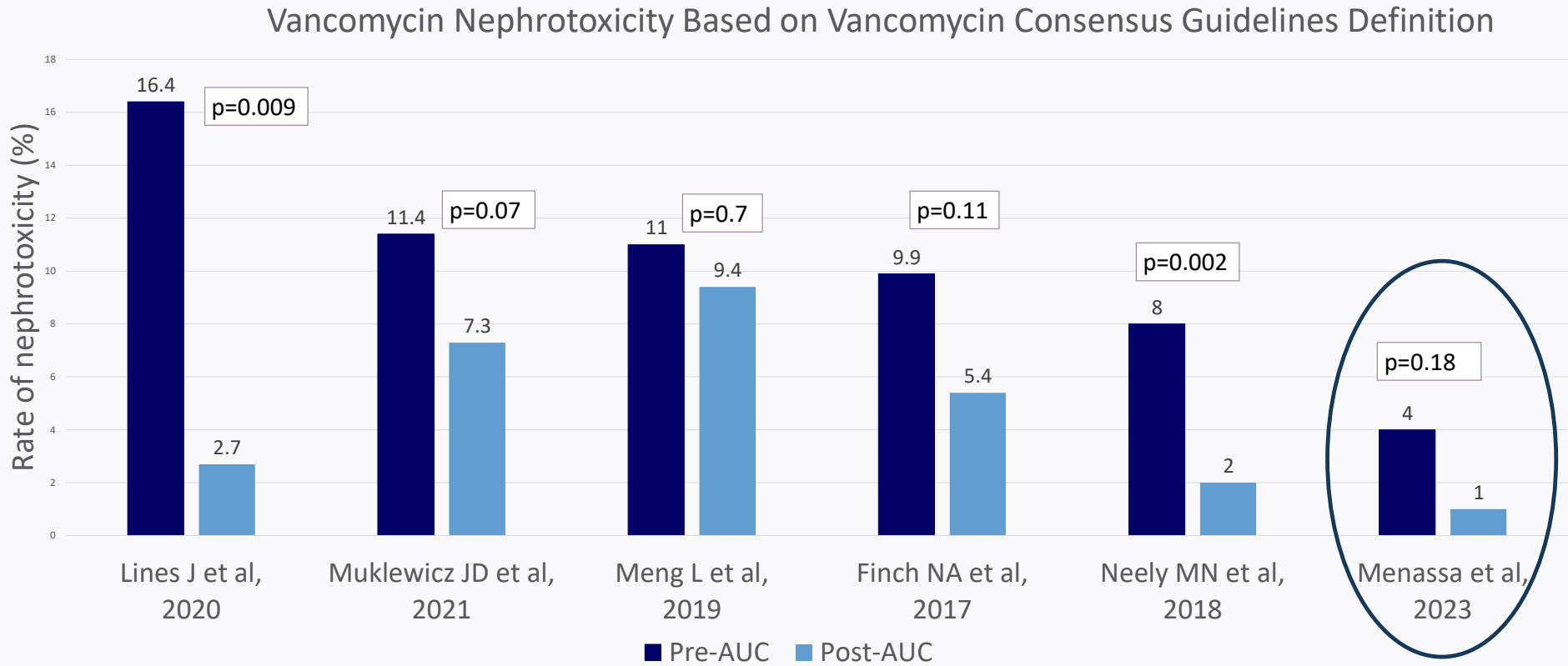
VANCOMYCIN AUC RESEARCH PROJECT

- Methods
  - Retrospective cohort study in adult hospitalized patients who qualify for AUC-based monitoring
  - Pre- and post-AUC cohort
- Objective
  - Assess the impact of vancomycin AUC-guided monitoring strategy on treatment safety and efficacy before and after its implementation among hospitalized adult patients

STUDY ENDPOINTS

- Primary Safety Endpoint
  - Rate of vancomycin-associated toxicity in the two groups
- Secondary Efficacy Endpoint
  - Clinical efficacy using a validated tool taking into consideration signs and symptoms, set laboratory parameters, and cultures
- Cost Analysis
  - Takes into account the cost of vancomycin therapy and cost of levels withdrawn

PRIMARY SAFETY OUTCOME



Finch NA et al. Antimicrobial Agents Chemother. 2017; Muklewicz JD et al. Int J Antimicrobial Agents.2021; Meng L et al. *Pharmacotherapy*.2019; Neely MN et al. Antimicrobial Agents Chemother. 2018; Lines J et al. *Int J Clin Pharmacol*. 2021

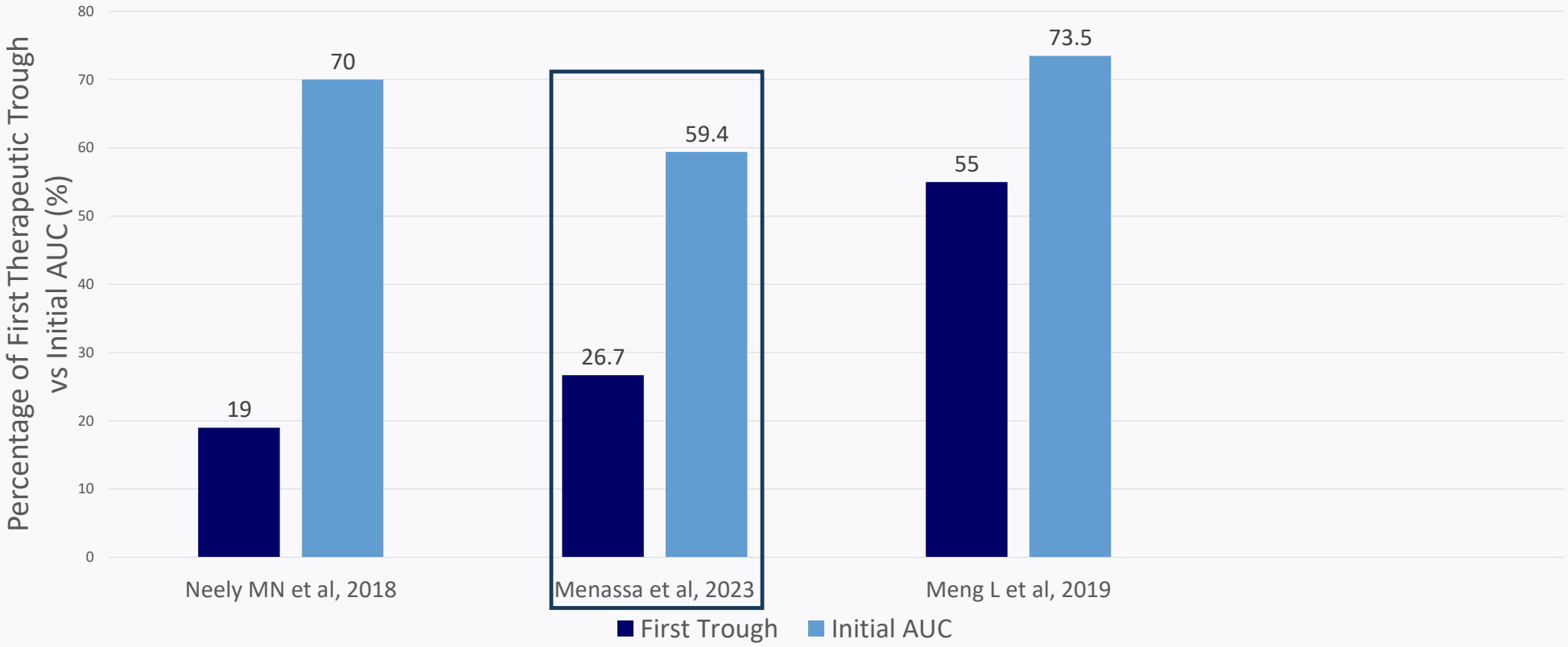
EFFICACY OUTCOME

Efficacy	Pre-AUC Cohort (n= 95)	Post-AUC Cohort (n=108)	p-value
Success n*(%)*	6 (6.3)	10 (9.3)	
Improvement n*(%)*	87 (91.6)	98 (90.7)	0.27
Failure n*(%)*	2 (2.1)	0 (0)	

- Efficacy outcomes comparable to other studies
- Effect not expected to be significant because of high trough targets in pre-AUC cohort

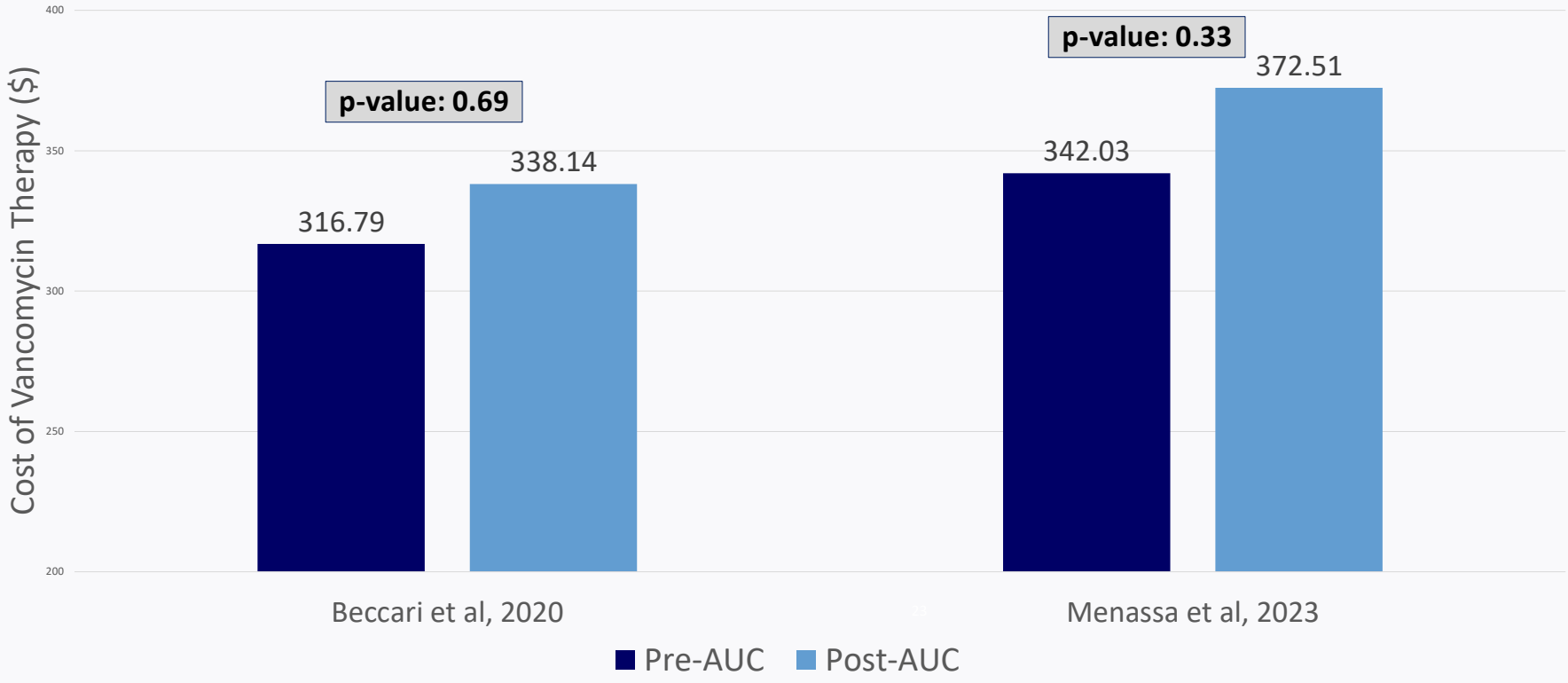
Eads AV et al, J Pharm Pract. 2022 Oct;35(5):680-685;Neely MN et al. Antimicrobial Agents Chemother. 2018; 62 (2): 2042-17

APPROPRIATENESS OF FIRST TROUGH VERSUS INITIAL AUC



Neely MN et al. Antimicrobial Agents Chemother. 2018; 62 (2): 2042-17; Meng L et al. *Pharmacotherapy*.2019; 39(4): 433-442

COST ANALYSIS – TOTAL VANCOMYCIN THERAPY COST



Beccari MV et al. *J Am Pharm Assoc* 2020; 60(5):729-733

SUGGESTED SOLUTIONS TO ARISING CHALLENGES

- Extensive training to be provided to all staff with more reliance on pharmacy input
- Emphasis on accuracy of taking levels at the right time to avoid unnecessary added costs
- Concerns with adjustment of levels when troughs are ”traditionally low”

KEY TAKEAWAYS

- Vancomycin AUC-based monitoring is the recommended strategy for patients maintained on vancomycin
- AUC-guided monitoring was associated with better clinical outcomes, more appropriate levels taken, lower nephrotoxicity, and less exposure to vancomycin
- Readily-available tools facilitate AUC-guided monitoring
- Education and training of all healthcare providers is key to a successful implementation of an AUC-based monitoring strategy

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THANK YOU

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ANY QUESTIONS?

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